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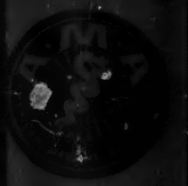

A.M.A. ARCHIVES OF INTERNAL MEDICINE

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Louis P. Jervey Jr. and Morton Hamburger

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Carbohydrate Metabolism in Brain Disease

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VIII. Carbohydrate Metabolism in Wernicke's Encephalopathy Associated with Alcoholism
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References: **1.** Rosenberg, H. N., and Michelson, A. L.: Am. J. M. Sc. *230*:254 (Sept.) 1955. **2.** Kory, R. C., *et al.*: Am. Heart J. *50*:308 (Aug.) 1955. **3.** Winsor, T., and Humphreys, P.: Angiology *3*:1 (Feb.) 1953. **4.** Plotz, M.: New York State J. Med. *52*:2012 (Aug. 15) 1952. **5.** Dailheu-Geoffroy, P.: L'Ouest-Médical, vol. 3 (July) 1950.

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A. M. A.
ARCHIVES OF INTERNAL MEDICINE

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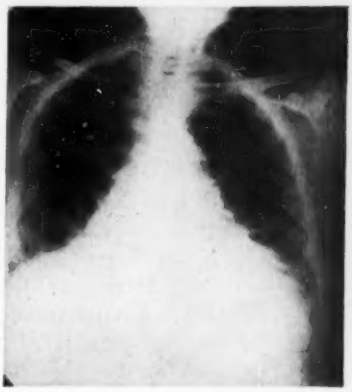

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1. Abramson, Julius; Bresnick, Elliott; and Sapienza, P.L.: *New England Jour. Med.*, 243:44, July 13, 1950.
2. Conybeare, John; and Mann, W.N.: Textbook of Medicine. Edinburgh, E. & S. Livingstone Ltd., 10th ed., 1952, p. 443.

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New Cover Design

With this issue, the A. M. A. Archives of Internal Medicine presents a new cover design and a slight modification of page format.

Two elements contribute to an attractive cover—simplicity and cleanliness. We believe that we have obtained the two primary objectives necessary in a cover design of this nature: namely, that it is attractive and that it conveys the subjective feeling of the unit which it represents, as well as legibility, which is important in this case because of the contents listing involved. This cover is fluid enough to attractively accommodate varying lengths of contents listing. By the use of a simple line or block treatment, and by placing the contents upon a white background, we gain the maximum contrast possible, therefore, greater legibility.

The use of the seal has several functions: Being a circle in design, it relieves to an extent the over-all use of lines, squares, and rectangles; it stands as a symbol for the many years of dedicated service by an organization of the American Medical Association's stature in the advancement of knowledge in specialized fields, thus adding immeasurably to the effectiveness of the design.

The change in page format is confined to the title, subtitle, and authors' names. The change from a Coronet Bold type face to Bodoni Bold will eliminate the difficulty encountered when reading a formula or an abbreviation in script capitals. The use of Antique Italic for subtitles and Spartan Bold for the authors creates a desirable distinction between these parts. The arrangement realizes a saving in space.

This new cover is a development of an idea. It is not the result of a sudden thought. First, a suggestion was presented which was nothing more than a different arrangement of familiar elements. Then followed the collection of reactions, suggestions, and additional experimentation in search for the inspiration. All of the separate bits of information gathered were thoroughly digested, and the relationship between elements was established. The result is the crystallization of the idea. In following this procedure, our readers and editors have contributed immeasurably to the end product. Their cooperation means a new design of lasting quality.

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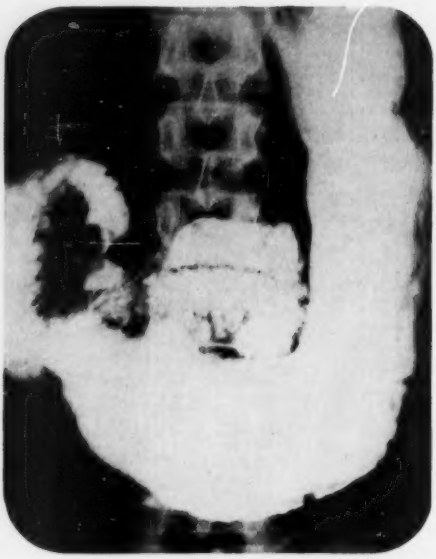

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*Roentgenograms courtesy of I. Richard Schwartz, M.D., Kings County Gastrointestinal Clinic, Brooklyn, N.Y.

SEARLE

A.M.A. ARCHIVES OF
INTERNAL MEDICINE

The Treatment of Acute Friedlaender's Bacillus Pneumonia

A Continuing Problem

LOUIS P. JERVEY Jr., M.D., and MORTON HAMBURGER, M.D., Cincinnati

The monumental advances in the therapy of pneumococcal pneumonia over the past 15 years have given the physician a justified confidence that with modern antibiotics the outcome of a case of pneumonia will usually be favorable. Caution is needed lest we apply this confidence uncritically to every case and thereby relax in our efforts to discover uncommon but stubborn bacterial species which may infect the lung. Acute Friedländer's bacillus * pneumonia, though accounting for only a small percentage of such infections, still carries a sufficiently high mortality to make imperative its early recognition and the early institution of appropriate therapy.

The ocurrence of a number of fatal cases of acute Friedlander's bacillus pneumonia at the Cincinnati General Hospital during recent years, despite seemingly adequate antibiotic treatment, has prompted us to analyze our experience with this disease.

Material and Methods

Hospital records of all cases of pulmonary infection due to Klebsiella pneumoniae from 1939 to 1956 were reviewed. However, since the purpose of the review was to evaluate the treatment of acute primary Friedländer's bacillus pneumonia, the following types of cases were excluded: (1) infections limited to the bronchial tree as judged by x-ray and clinical evaluation; (2) instances in which patients suffering from primary diseases, such as carcinoma or the end stages of congestive heart failure, developed K. pneumoniae infection as a secondary event; (3) cases which showed a favorable response to penicillin despite the presence of K. pneumoniae in the sputum culture; (4) chronic Friedländer's bacillus pneumonia; and (5) empyema due to K. pneumoniae when this complication was present at the time of admission.

A total of 30 cases of acute primary Friedländer's bacillus pneumonia remained. Friedländer's bacilli were recovered from the following sites: blood and sputum, 14 cases; blood and postmortem lung cultures, 1 case; postmortem lung culture, 2 cases; sputum and postmortem lung culture, 3 cases; sputum only, 10 cases. Autopsies were performed on 17 of the 19 fatal cases.

K. pneumoniae and pneumococci were present simultaneously in the sputum of five patients but in no instance was the pneumococcus cultured from the blood stream.

Typing of the organisms with specific rabbit antiserum was performed in our laboratory in 22 cases. Sixteen of these were Type A and 6, Type B. Three strains were sent to the Communicable Disease Center, Chamblee, Ga., for identification. One of these (from Case 27) was identified as Type E. In a second case (Case 28) the organism from the blood culture was identified as Type B, while the sputum yielded a Klebsiella, Type 17. In the third case (Case 29) Klebsiella, Type 17, was identified from the sputum while the blood yielded a motile Aerobacter species—lactose-positive, agglutinated by Klebsiella Types 8, 11, and 21. We are at a loss to explain this discrepancy.

Submitted for publication June 29, 1956.

* The terms Friedländer's bacillus and Klebsiella pneumoniae will be used interchangeably in this article.

From the Infectious Disease Laboratory, Department of Medicine, University of Cincinnati College of Medicine and the Cincinnati General Hospital.

The in vitro sensitivity of the organism to one or more antibiotics was determined in nine cases. These tests were done by a twofold serial dilution technique described previously.[1]

Results

Mortality in the "Prestreptomycin Era" and the "Era of 'Modern' Chemotherapy"

The number of cases admitted each year and the corresponding mortality are summarized in Table 1. The Table is divided into two sections, the upper section including those cases treated prior to 1948 and the lower, those treated thereafter. This point of division was selected because 1948 was the first year in which streptomycin was employed in this series. Prior to that year, treatment consisted mainly of sulfonamides. After 1948, recognized cases began to receive streptomycin, tetracycline drugs,† or combinations of these with sulfonamides. An interesting coincidence is that each section of Table 1 covers a period of eight years, and the total number of cases for each period is the same.

TABLE 1.—*Mortality in Friedländer's Bacillus Pneumonia at the Cincinnati General Hospital from 1939 to 1956*

Year	No. of Cases	Died	
1939	3	3	
1940	2	1	
1941	1	1	
1942	2	2	
1943	2	1	
1944	2	1	
1945	1	0	
1946	1	1	
1947	1	1	
Total	15	11	Mortality, 73%
1948*	3	3	
1949	2	0	
1950	1	0	
1951	1	0	
1952	1	1	
1953	2	2	
1954	2	2	
1955	2	0	
1956	1	0	
Total	15	8	Mortality, 53%
Total for series	30	19	Mortality, 63%

*First year in which treatment with streptomycin was employed in this series.

There seemed to be a decline in the mortality rate from 73% in the first period of the study to 53% in the second. Each group, of course, includes patients who received no specific therapy, patients who died after small amounts of drugs were administered, and patients to whom improper therapy was given. Still, the over-all figures for each period speak for themselves in depicting the continuing gravity of this type of infection.

Prestreptomycin Era.—Table 2 presents summaries of pertinent clinical information on cases admitted from 1939 through 1947, corresponding to the upper division of Table 1. Arrangement is in accordance with whether the patient survived or died rather than in strict chronologic order.

It will be noted that all patients were treated with sulfonamides, with the exception of Case 10, who received no treatment. This patient was thought to have bronchiogenic carcinoma until the diagnosis of Friedländer's bacillus pneumonia was made at autopsy. In addition to sulfonamides, Case 9 received Type A Friedländer's rabbit antiserum.

Four (27%) of these patients survived. Each was treated with sulfonamides and received at least 7 gm. in the first 24 hours. However, amounts of drug in this range were given during the same period to over half of the fatal cases without avail.

The average age of the survivors was 52 years, as compared to 49 years in the fatal cases. None of the survivors had bacteremia, while blood cultures were positive in every fatal case where they were drawn. The disease involved multiple lobes in 2 patients who lived and in 10 who died. Lung abscesses developed in two patients in each group. The patients who recovered improved slowly, none showing complete clearing of the infiltrate prior to discharge from the hospital.

Follow-up on the surviving cases was not very satisfactory. Case 12 was not seen until five years later, when he died of a subarachnoid hemorrhage associated with hypertension. Interim history, although in-

† The chlortetracycline used in this study was Aureomycin supplied by Dr. Stanton M. Hardy, of the Lederle Laboratories Division, American Cyanamid Company.

TABLE 2.—*Fifteen Cases of Friedländer's Bacillus Pneumonia Treated from 1939-1947*

Case and Date Admitted	Age & Sex	Day of Disease on Entry	Cultures* Sp.	Bl.	P.M.L.	No. Lobes	Lung Abscess	Drug†	Hosp. Days Given	Dose First 24 Hrs.‡	Total Dose‡	Route	Outcome
1 12/9/39	35 M	1	Fr. B	Fr. B	Fr. B	5	0	SPD	1-2	2	4	Oral	Died 33 hr.
2 1/19/39	54 M	9	Fr. A Pn 15	Fr. A	Fr. A	1	+	SPD	4-9	0	25	Oral	Died 9th hosp. day
3 1/11/39	63 M	7	Fr. A	Fr. A	Fr. A	2	+	SPD	2	0	3	Oral	Died 2d hosp. day
4 4/6/40	35 M	3	Fr. A	Fr. A	Fr. A	2	0	STZ	1-7	14	94	Oral	Died 7th hosp. day
5 5/18/41	47 M	4	Fr. A	Fr. A	N.D.	3	0	SDZ	1	10	10	Oral	Died 16 hr.
6 11/21/42	47 M	14	Fr. A	Fr. A	N.D.	3	0	STZ	1	9	9	I.V. + oral	Died 6½ hr.
7 7/20/42	55 F	?	Fr. A	Fr. A	N.D.	5	0	STZ	1	7	7	Oral	Died 15½ hr.
8 2/22/43	40 M	17	Fr. A	Fr. A	N.D.	3	0	SDZ	1	6	6	I.V.	Died 9 hr.
9 11/12/44	59 M	2	Fr. Pn 31	Fr. A	Fr. A	5	0	SMZ Ser.	1-2 2	6 --	7 18.5 ml.	Oral I.V.	Died 29½ hr.
10 11/1/46	63 F	?	N.D.	N.D.	Fr. A	3	0	0	--	0	--	--	Died 31 hr.
11 11/5/49	42 M	11	Fr.	Fr.	Fr.	3	0	PNC SMC	1 1	0.12 4	0.12 4	I.M. Oral	Died 10 hr.
12 11/12/40	55 M	4	Fr. A	Neg.	N.D.	2	0	SPD STZ	1-4 11-21	7 ..	24 60	Oral Oral	Disch. 23d hosp. day
13 2/24/43	54 M	2	Fr. A PN 27 PN 29	Neg.	N.D.	1	0	STZ	1-12	9	91	Oral	Disch. 16th hosp. day
14 8/28/44	37 M	3	Fr. B	Neg.	N.D.	3	+	SMZ SDZ	1-13 24-30	8 ..	53 34	Oral Oral	Disch. 52d hosp. day
15 7/16/45	62 F	3	Fr. A	Neg.	N.D.	1	+	SMZ	1 30	7	81	Oral	Disch. 98th hosp. day

*Sp. indicates sputum; Bl., blood; P.M.L., postmortem lung culture; Fr. A, Klebsiella pneumoniae Type A; Fr. B, K. pneumoniae Type B; Fr., K. pneumoniae untyped; Pn. 15, Pneumococcus Type 15 (etc.); N.D., not done; Neg., negative.
†SPD indicates sulfapyridine; STZ, sulfathiazole; SDZ, sulfadiazine; SMZ, sulfamerazine; PNC, penicillin; Ser., type-specific Friedländer's antiserum.
‡All doses are expressed in grams except penicillin, which is expressed in million units.

adequate, revealed no prominent respiratory symptoms. Chest x-ray was not obtained, and permission for autopsy was not granted. Case 13 showed continued clinical and x-ray improvement during a two months' clinic follow-up but was not seen thereafter, and Case 14 had no respiratory complaints when seen two years later for another ailment. Case 15 was left with a persistent lung abscess due to K. pneumoniae following the acute episode.

Eleven (73%) of these patients died. The course of the fatal infections was always progressively downhill, death occurring 2 to 18 days after onset of the disease. Five of the deaths occurred within the first 24 hours after admission and another four within the first 48 hours.

Era of "Modern" Chemotherapy.—Table 3 summarizes pertinent clinical information on the 15 patients admitted from 1948 through April, 1956, corresponding to lower division of Table 1. In four patients of this group (Cases 16, 18, 19, and 20) the diagnosis was not made during life, and treatment was accordingly inadequate. The remaining cases were treated with varying combinations of streptomycin, penicillin, tetracycline drugs, and sulfonamides. Two

TABLE 3.—*Fifteen Cases of Friedländer's Bacillus Pneumonia Treated from* 1948-1956

Case and Date Admitted	Age & Sex	Day of Disease on Entry	Cultures* Sp.	Bl.	P.M.L.	No. Lobes	Lung Abscess	Drug†	Hosp. Days Given	Dose First 24 Hr.‡	Total Dose‡	Route	Outcome
16 1/24/48	73 M	?	Fr.	Fr.	N.D.	2	0	PNC	1	0.025	0.025	I.M.	Died 7 hr.
17 5/5/48	64 M	3	PN 15	Fr.	Fr.	1	0	PNC SDZ SMC	1-2 1 1-2	0.9 1 2.5	0.9 1 2.5	I.M. Oral I.M.	Died 27 hr.
18 6/20/48	60 M	3	N.D.	N.D.	Fr.	3	0	0	--	--	--	--	Died 11 hr.
19 3/4/52	60 M	4	Fr. A	Neg.	Fr. A	3	0	PNC	1-3	0.9	1.8	I.M.	Died 3d hosp. day
20 3/14/53	42 M	?	PN 22 Fr.A	N.D.	Fr.	1	0	PNC GNC	1-2 1-2	0.8 6	1.2 9	I.M. Oral	Died 2d hosp. day
21 8/1/53	46 M	?	Fr. B	Neg.	Fr.	5	+	PNC SMC AMC PMX	1-4 1-14 5-14 12-14	0.9 3	2.7 13 9 0.3	I.M. I.M. Oral I.M.	Died 14th hosp. day
22 6/15/54	43 M	6	Fr. B	Fr. B	Neg	2	+	PNC SMC GNC AMC PMX	1 1-23 1-27 1-6 9-16	1.2 2.5 5 0.5 ..	1.2 45.5 159 10 0.98	I.M. I.M. Oral Oral & I.V. I.M.	Died 28th hosp. day
23 9/8/54	66 M	7	Fr. A	Neg.	N.D.	2	0	PNC SMC AMC GNC	1 1 1 1	0.3 1 1.5 4	0.3 1 1.5 4	I.M. I.M. I.V. Oral	Died 19 hr.
24 12/3/49	44 M	6	Fr.	Neg.	N.D.	1	0	AMC	1-5	1.5	8.5	Oral	Disch. 10th hosp. day
25 12/27/49	51 M	2	Fr. A	Neg.	N.D.	2	0	SDZ SMC AMC	1-4 1-14 1-14 18-21	9 1.5 9	24 14 96	Oral I.M. Oral	Disch. 22d hosp. day
26 6/22/50	44 M	3	Fr. B	Neg.	N.D.	3	0	PNC SDZ SMC AMC	1-16 1-20 1-8 10-14 1-20	0.8 5 3 0.5	11.4 107 20 36	I.M. Oral I.M. Oral	Disch. 22d hosp. day
27 10/13/51	68 M	3	Fr. E	Neg.	N.D.	3	0	PNC GNC TMC	1-4 4-17 1-17	1.2 .. 0.75	3.2 80 24	I.M. Oral Oral	Disch. 40th hosp. day
28 6/21/55	43 M	3	Fr. 17	Fr. B	N.D.	2	0	PNC SMC TCL GNC	1-7 2-56 2-63 2-63	1.5 0 0 0	12.6 61 122 552	I.M. I.M. I.M. & oral I.M. & oral	Disch. 79th hosp. day
29 7/20/55	42 M	2	PN 3 Fr. 17	§ 	N.D.	1	0	TMC SMC GNC	1-39 1-21 1-21	1.85 3.5 4	40 I.V., I.M. Oral 23 126	I.V., oral	Disch. 40th hosp. day
30 4/8/56	50 F	3	Fr. B	Neg.	N.D.	1	+	SMC TCL SDZ CMC	1-20 1-20 1-34 20-34	3 1.8 8 ..	29 40 204 28	I.M. I.M., oral I.V., oral Oral	Left hosp. 34th day

*Sp. indicates sputum; Bl., blood; P.M.L., postmortem lung culture; Fr. A, Klebsiella pneumoniae Type A; Fr. B, K. pneumoniae Type B; Fr. 17, K. pneumoniae Type 17; Fr., K. pneumoniae untyped; PN 15, pneumococcus Type 15 (etc.); N.D., not done; Neg. negative.

†PNC indicates penicillin; GNC, sulfisoxazole (gantrisin); SMC, streptomycin; AMC, chlortetracycline; SDZ, sulfadiazine; PMX, Polymyxin B (Aerosporin) sulfate; TMC, oxytetracycline; TCL, tetracycline; CMC, chloramphenicol.

‡All doses are expressed in grams except penicillin, which is expressed in million units.

§Motile Aerobacter species, lactose-positive, agglutinated by Klebsiella Types 8, 11, and 21.

cases received polymyxin B sulfate * in addition.

Seven (47%) of these patients survived. All received a tetracycline drug, and five, streptomycin also. Tetracycline drugs were given in the first 24 hours to six of the seven survivors, although some patients re-

* The polymyxin B was Aerosporin, supplied by Burroughs Wellcome & Company, Inc., through the courtesy of Dr. D. S. Searle.

ceived only small amounts. Only two of the eight fatal cases received a tetracycline drug during this period. Four patients in each group received streptomycin in the first 24 hours. Significant amounts of sulfonamides were administered on the first day to three of the fatal cases and four of the survivors.

A few clinical data are of interest. The average age of the survivors was 49 years, compared to 57 years in the fatal cases. Bacteremia occurred in two of the survivors and in three of the fatal cases. The disease involved multiple lobes in four of the patients who lived and in six who died. Lung abscesses developed in one of the survivors and in two fatal cases. The patients who recovered improved slowly, and in none was there complete clearing of the chest x-ray prior to discharge.

Follow-up in the seven survivors leaves much to be desired. Case 24 never returned to the outpatient clinic following discharge from the hospital, and Case 26 was seen in the clinic only once, one month following discharge. He was asymptomatic at this time, but chest x-ray was not obtained. Case 25 died of postnecrotic cirrhosis and pneumococcal (Type 14) pneumonia one year after his discharge from the hospital; no residua of Friedländer's bacillus infection were noted at autopsy. Case 27 has been followed regularly in the clinic. For over two years after his infection he has continued to have an intermittent productive cough and x-ray evidence of bilateral "strand-like" densities in both midlung fields. Sputum culture is negative for K. pneumoniae. Case 28 was last seen in November, 1955, when he was largely asymptomatic, but x-ray still showed residual pulmonary infiltrate. Cases 29 and 30 have never returned for follow-up.

Eight (53%) of these patients died. Of the four undiagnosed cases, one received no treatment (Case 18), two received penicillin alone (Cases 16 and 19), and one received penicillin and sulfisoxazole (Gantrisin) (Case 20). Two patients (Cases 17 and 23) died quickly after relatively small amounts of drugs were given. On the other hand, Case 21 survived 14 days and died of the infection despite intensive treatment. Case 22 survived 28 days, only to die of renal complications of the infection, and perhaps its treatment. In contrast is Case 24, where recovery followed a total dose of only 8.5 gm. of chlortetracycline.

As was the case in the "Prestreptomycin Era," the course of the fatal infections was usually progressively downhill. Three of the eight fatalities occurred within the first 24 hours after admission and two more within the first 48 hours.

In Vitro Sensitivity of Strains of K. Pneumoniae to Six Antibiotics

The in vitro sensitivity of K. pneumoniae to a number of antibiotics is presented in Table 4.

Every strain tested was resistant to penicillin and sensitive to streptomycin. One strain was highly resistant and two moderately resistant to chloramphenicol. All were moderately sensitive to tetracycline drugs. All strains tested were inhibited by 5 γ/milliliter or less of polymyxin B.

TABLE 4.—*In Vitro Sensitivity of Klebsiella Pneumoniae to Six Antibiotics*

Case	Antibiotic*						
	PNC	SMC	AMC	TMC	TCL	CMC	PMX
17	----	0.05	----	----	----	----	----
19	>25.0	<1.25	1.0	2.0	----	3.9	0.2
20	----	<0.12	3.9	----	----	15.6	<0.02
21	----	1.0	7.8	----	----	125.0	5.0
22	>25.0	0.5	7.8	----	----	7.8	0.025
23	25.0	0.5	3.9	----	----	2.0	----
25	----	0.02	0.2	----	----	0.4	----
27	----	<1.25	1.0	3.9	----	2.0	----
30	----	0.25	----	----	3.9	15.6	----

*PNC indicates penicillin; SMC, streptomycin; AMC, chlortetracycline; TMC, oxytetracycline; TCL, tetracycline; CMC, chloramphenicol; PMX, polymyxin B (Aerosporin) sulfate. All results are expressed as minimal inhibiting concentration in γ/milliliter.

TABLE 5.—*Reported Mortality in Acute Friedländer's Bacillus Pneumonia*

Year	Author	No. Cases	Mortality per Cent	Treatment*
1937	Solomon[2]	32	97	Serum in 5
1937	Bullowa, Chess, & Friedman[3]	41	83	Serum in 8
1941	Perlman & Bullowa[4]	37	84	Serum and/or Sulfa in 29
1950	Nataro, Shapiro, & Gordon[5]	5	20	SMC in 4; AMC in 1
1951	Gill[6]	15	53	Sulfa in 8
1951	Kirby & Coleman[7]	11	55	CMC, AMC, SMC, & Sulfa†
1952	Barber & Grant[8]	6	33	CMC, SMC, & Sulfa in 5†

*Serum indicates type-specific Friedländer's antiserum; Sulfa, sulfonamides; SMC, streptomycin; AMC, chlortetracycline; CMC, chloramphenicol.
†Used alone or in varying combinations.

Comment

The severity of untreated Friedländer's bacillus pneumonia has long been recognized, as the data in Table 5 attest. Inasmuch as reported mortality in the chronic form of the disease[9] is considerably lower than in the acute, only acute cases are included in the Table.

There has evidently been a decrease in the mortality since 1950. Kirby and Coleman,[7] in 1951, reported 11 cases of acute Friedländer's bacillus pneumonia, with 6 deaths. These patients received streptomycin, chlortetracycline, or chloramphenicol, alone or in combination. Four deaths occurred within 24 hours despite treatment with antibiotics comparable to those used in the survivors. From the small number of patients it was not possible to draw final conclusions as to the relative value of various antibiotics used; it did seem that chlortetracycline and chloramphenicol were probably comparable to streptomycin in their effect.

Barber and Grant,[8] in 1952, reported six cases of acute pneumonia due to Friedländer's bacillus, one of whom died before treatment was started. The remaining five were given streptomycin. Four of the five recovered; the one who died received chloramphenicol in addition. None of the specified drugs were administered to any patient in the first 24 hours of hospitalization. Instead, the patients received penicillin, alone or with sulfonamides, for 24 hours to 21 days before more specific therapy was given. We can only conclude that there is a tremendous individual variation in resistance to the infection regardless of therapy given.

From our cases we gain the following impressions: (1) that a high fatality rate ensues with either no therapy or with penicillin only; (2) that treatment with sulfonamides represents a slight improvement over this; (3) that treatment with the tetracycline drugs or streptomycin represents a still further improvement, and (4) that there may be some added advantage to the early use of tetracycline drugs in treatment.

It is interesting that of the 15 bacteremic patients in our series, only 2 survived the infection, and these were both in the "modern treatment" group. This observation is in contrast to that of Solomon,[2] who noted that bacteremia did not influence the mortality in this disease. It is also interesting that blood cultures were positive in 71% of our cases where they were drawn in the group treated before 1948, while the incidence fell to 38% in the 1948-1956 group.

Single or multiple lung abscesses developed in 7 of our 30 cases. Four patients were under treatment with sulfonamides at the time of x-ray appearance and three under treatment with streptomycin and tetracycline drugs. Survivors from each treatment group showed evidence of residual chronic pulmonary involvement.

It is essential to distinguish Friedländer's pneumonia from pneumococcal pneumonia as early as possible so that therapy other than penicillin may be instituted. Differentiation on clinical grounds alone may be impossible. Diagnosis may be made earliest by finding the organism in a Gram-stained smear of the sputum. If typing serum is available, a more specific diagnosis can be made by direct typing of the organisms from the sputum.

We feel that until a more effective agent is discovered for the treatment of this disease, the patient is offered the best opportunity for survival when treated early with a combination of antibiotics. We currently use a combination of a tetracycline drug (2 gm. per day), streptomycin (2 gm. per day), and a sulfonamide (4-6 gm. per day).

Although the antibiotic sensitivity of different strains of K. pneumoniae may vary, most strains are sensitive to streptomycin and the tetracycline drugs. On the other hand, resistance to streptomycin may develop while treatment with this agent is in progress.[10] Hence, in vitro sensitivity studies become an important guide in the management of a given case. Under no circumstances should therapy be withheld until the results of such studies are available.

In contrast to the uniformly good results achieved in the treatment of pneumococcal pneumonia, the high mortality in Friedländer's pneumonia, despite treatment with drugs quite effective in vitro, represents a continuing challenge. Undoubtedly the thick, tenacious exudate which occurs in this infection plays a role in hindering the efficacy of presumably adequate chemotherapeutic drugs. Perhaps the addition of some yet to be discovered mucolytic agent will further reduce the mortality.

Summary

Thirty cases of acute Friedländer's bacillus pneumonia were admitted to the Cincinnati General Hospital between 1939 and 1956. The mortality in the 15 cases treated prior to 1948 was 73%, whereas that in the patients treated subsequent to 1948 was 53%. Though this difference is not statistically significant, the decrease, when considered in conjunction with similar experience in other hospitals, indicates that modern treatment improves the outlook in this still very serious infection. Penicillin is of no value whatever. Sulfonamide treatment seems a little more effective, and treatment with streptomycin and tetracycline drugs, better still.

Bacteremia was associated with a very high mortality. The only 2 survivors among 15 bacteremic cases were treated with a combination of streptomycin, a sulfonamide, and a tetracycline drug.

Lung abscesses developed in four of the sulfonamide-treated cases and in three of the cases treated with newer antibiotics. Survivors in each treatment group showed evidence of residual pulmonary disease.

Until a more effective agent is discovered for the treatment of this disease, we recommend a combination of a tetracycline drug, streptomycin, and a sulfonamide in every case.

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REFERENCES

1. Hamburger, M., and Muething, D.: The in Vitro Sensitivity to 8 Antibiotics of Streptococci and Staphylococci Recovered from Cases of Bacterial Endocarditis, J. Lab. & Clin. Med. 37:60 (Jan.) 1951.

2. Solomon, S.: Primary Friedländer Pneumonia: Report of 32 Cases, J. A. M. A. 108:937 (March 20) 1937.

3. Bullowa, J. G. M.; Chess, J., and Friedman, N. B.: Pneumonia Due to Bacillus Friedländeri: A Report on 41 Patients, with Consideration of Specific Serum Therapy, Arch. Int. Med. 60:735 (Nov.) 1937.

4. Perlman, E., and Bullowa, J. G. M.: Primary Bacillus Friedländer (Klebsiella Pneumoniae) Pneumonia: Therapy of B. Friedländer B Pneumonia, Arch. Int. Med. 67:907 (May) 1941.

5. Nataro, M.; Shapiro, D., and Gordon, A. T.: Acute Primary Klebsiella Pneumonia, J A. M. A. 144:12 (Sept. 2) 1950.

6. Gill, R. J.: Treatment of Friedländer's Pneumonia, Am. J. M. Sc. 221:5 (Jan.) 1951.

7. Kirby, W. M. M., and Coleman, D. H.: Antibiotic Therapy of Friedländer Pneumonia, Am. J. Med. 11:179 (Aug.) 1951.

8. Barber, J. M., and Grant, A. P.: Friedländer's Pneumonia: A Report on 6 Cases, Brit. M. J. 2:752 (Oct. 4) 1952.

9. Solomon, S.: Chronic Friedländer Infections of the Lungs; Report of 17 Cases and Observations on Therapy with Sulfapyridine and Sulfanilamide, J. A. M. A. 115:1527 (Nov. 2) 1940.

10. Finland, M.; Murray, R.; Harris, H. W.; Kilham, L., and Meads, M.: Development of Streptomycin Resistance During Treatment, J. A. M. A. 132:16 (Sept. 7) 1946.

The Circulating Red Blood Cell Volume

I. Its Relationship to the Peripheral Blood Cell Counts in Normal Subjects and Persons with Polycythemia

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Introduction

The measurement of the concentration of hemoglobin or erythrocytes in the peripheral blood is probably one of the most widely employed laboratory aids in clinical medicine. Interpretation of these measurements is based upon widely used standards for normal values which were obtained by statistical studies of large groups of persons in many geographical areas.[1] The impression of the existence of anemia or polycythemia is given when values obtained are respectively lower or higher than those accepted standards.

An investigation of the relationship between the peripheral blood cell counts and the total body red cell volume was undertaken in a variety of clinical states. The present study deals with this correlation in a group of normal subjects and in patients with elevated erythrocyte values.

Methods

The subjects studied were patients on the wards or attending the hematology clinic at Kings County Hospital. They were selected on the basis of the following criteria: Group I—with no hematologic abnormalities. Group II—known patients with includes some persons who were supposedly well controlled by therapy and others who were untreated at the time of this study. Group III—patients with high peripheral red blood cell values, some of whom were suspected of having polycythemia vera prior to the tests.

The pertinent measurements made on each subject included spectrophotometric determination of hemoglobin concentration, using an alkali-globin method, enumeration of the erythrocytes, determination of the hematocrit,[2] measurement of the polycythemia vera of varying severity. This group weight, and a determination of the total body red cell volume by use of a modification of Reeve and Veall's method employing P^{32}-labeled red cells.[3]

Seven cubic centimeters of venous blood was incubated sterilely at 37 C for two hours with approximately 150-200 μc of P^{32} (sodium radiophosphate, Abbott Laboratories). After three washes with isotonic saline solution and reconstitution to the original hematocrit, 1-2 cc. of the tagged erythrocytes were readministered to the patient intravenously. An identical aliquot of the tagged cells was inoculated into a 2000 cc. volumetric flask and diluted to volume with tap water. After 10 minutes a sample of blood was removed from the other arm of the patient; the blood was hemolyzed with saponin and counted in the wet state in a planchet using a Beta sensitive Geiger-Müller tube (Tracerlab TGC-2). A similar quantity of the standard solution was treated in the same fashion with saponin and counted. The total circulating red blood cell volume (CRBCV) was calculated from the following formula:

$$\text{Cubic centimeters of CRBCV} = \frac{\text{counts/minute of standard} \times \text{dilution of standard (cc.)} \times \text{Hct\%}}{\text{counts/minute of blood sample}}$$

Calculations were made of circulating red blood cell volume per kilogram of body weight (CRBCV/kg.) and the ratio of hematocrit to red blood cell volume per kilogram (Hct/CRBCV/kg.).

Results

Group I.—This group (no hematologic abnormalities) included patients who were convalescing from minor infections and minor elective surgical procedures and some with no organic disease. The measurements made are recorded in Table 1. These patients varied from 10 to 80 years of age. Eleven of the twelve were males. The hematocrit values ranged from 40% to 50.5%. The circulating red blood cell vol-

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TABLE 1.—*Control Subjects*

Patient	Sex	Age	Weight, Kg.	HCT., per Cent*	CRBCV, Ml.†	CRBCV/Kg., Ml.‡	HCT./CRBCV/Kg.§
1	M	24	58.4	45	1,694	29.0	1.55
2	M	29	72.7	50.5	2,307	31.7	1.59
3	M	80	74.5	40.5	2,167	29.1	1.39
4	F	70	54.1	45	1,576	29.1	1.55
5	M	72	61.8	46.5	1,904	30.8	1.51
6	M	58	65.9	49	2,238	34.0	1.44
7	M	17	56.4	40	1,488	26.4	1.52
8	M	43	75.0	42	2,378	31.7	1.32
9	M	10	30.0	42.5	942	31.4	1.35
10	M	10	24.5	40	638	26.0	1.53
11	M	11	33.9	43	1,100	32.5	1.32
12	M	26	76.4	41	2,051	26.8	1.53
					Mean	29.9	1.47
						26.0-34.0	1.32–1.59
					Range	30±4	1.455±0.135

*HCT. indicates hematocrit of peripheral venous blood.
†CRBCV indicates circulating red blood cell volume.
‡Circulating red blood cell volume per kilogram of body weight.
§Hematocrit divided by circulating red blood cell volume per kilogram of body weight.

ume per kilogram of body weight varied in a range from 26.0-34.0 ml. with the mean value being 29.9 ml. The ratio of the hematocrit divided by the circulating red blood cell volume per kilogram of body weight in this group varied from 1.32 to 1.59, with a mean of 1.47.

Group II.—Nineteen patients with polycythemia vera were studied (Table 2). There were 13 men and 6 women patients in this group. The age span was from 31 to 76 years. The hematocrit ranged from 40% to 77%. The mean circulating red blood cell volume per kilogram was 49.1 ml., and the range was 36.6 to 77.2 ml. The ratio of the hematocrit to the CRBCV/kg. was found to average 1.21 and ranged from 0.83 to 1.54.

Group III ("Plethora").—There were seven persons in whom the hematocrit determinations were abnormally high, yet when studied, they were found to have normal values for CRBCV/kg. We have referred to the hematologic status as "Plethora" (Table 3). The four women in this group had hematocrit values of 50%-52%. The three men had hematocrit values of 52.5% to 59%. The CRBCV/kg. averaged 29.1 ml., with a range of 23.5 to 34.3. The ratio of Hct/CRBCV/kg. ranged from 1.65 to 2.13, with a mean of 1.82.

This was a heterogeneous group which included two persons with Addisonian pernicious anemia in remission following vitamin B_{12} therapy, one patient with congenital heart disease (the exact anomaly

TABLE 2.—*Polycythemia Vera*

Patient	Sex	Age	Weight, Kg.	HCT., per Cent*	CRBCV, Ml.†	CRBCV/Kg., Ml.‡	HCT./CRBCV/Kg.§
13	M	54	70.0	53	3,540	50.6	1.05
14	M	62	99.5	53	3,664	36.8	1.44
15	F	52	63.6	59	2,805	44.1	1.34
16	M	62	59.5	60	2,754	46.3	1.29
17	M	72	50.5	40	1,970	39.0	1.02
18	M	42	64.5	50	2,363	36.6	1.36
19	M	60	78.3	55	2,920	37.3	1.47
20	M	34	61.4	65	4,203	43.8	1.48
21	M	50	86.8	52	3,569	41.1	1.26
22	M	50	75.0	61	4,861	64.8	0.94
23	F	31	52.3	54	2,730	52.2	1.03
24	F	66	45.4	77	3,450	76.0	1.01
25	M	63	68.2	59	4,076	59.8	0.99
26	F	75	41.8	64	3,225	77.2	0.83
27	F	63	76.6	57	3,144	41.0	1.39
28	F	76	78.2	66	4,717	60.3	1.09
29	M	68	76.0	53	3,221	42.4	1.25
30	M	64	85.5	59	3,920	45.9	1.29
31	M	64	104.5	59	4,010	38.4	1.54
					Mean	49.1	1.21
						36.6–77.2	0.83–1.54
					Range	56.9±20.3	1.185±0.355

*HCT. indicates hematocrit of peripheral venous blood.
†CRBCV indicates circulating red blood cell volume.
‡Circulating red blood cell volume per kilogram of body weight.
§Hematocrit divided by circulating red blood cell volume per kilogram of body weight.

TABLE 3.—*"Plethora"*

Patient	Sex	Age	Weight, Kg.	HCT., per Cent*	CRBCV, Ml.†	CRBCV/Kg., Ml.‡	HCT./CRBCV/Kg.§
32	F	50	77.2	50	2,212	28.7	1.74
33	F	18	55.9	52	1,756	31.5	1.65
34	F	79	50.0	50	1,798	30.0	1.66
35	F	81	66.4	50	1,562	23.5	2.13
36	M	43	74.3	59	2,549	34.3	1.72
37	M	76	68.2	53	2,066	30.4	1.74
38	M	72	90.5	52.5	2,294	25.3	2.08
					Mean	29.1	1.82
					Range	23.5–34.3	1.65–2.13

*HCT. indicates hematocrit of peripheral venous blood.
†CRBCV indicates circulating red blood cell volume.
‡Circulating red blood cell volume per kilogram of body weight.
§Hematocrit divided by circulating red blood cell volume per kilogram of body weight.

is as yet undetermined), and one patient with severe dehydration secondary to prolonged vomiting. The remaining three patients were suspected of having polycythemia vera. This was not substantiated by any of the studies, and as far as it is known the only hematologic abnormality in these persons is the elevated venous hematocrit.

Comment

The method employed in this study for the determination of total body circulating red blood cell volume has been critically evaluated and has been accepted as valid by a variety of investigators.[3-7] The technical variables in the method, which include such things as the pipetting, injection, and counting errors, were periodically controlled. We found with measurements in vitro, using exactly the same technique as the in vivo studies with the substitution of a volumetric flask in lieu of a patient, that the above-mentioned factors could account for an error of at most 9.8%. The average error was only 3.0%.

The determination of the hematocrit is considerably more accurate than hemoglobin measurements or red blood cell counts. For

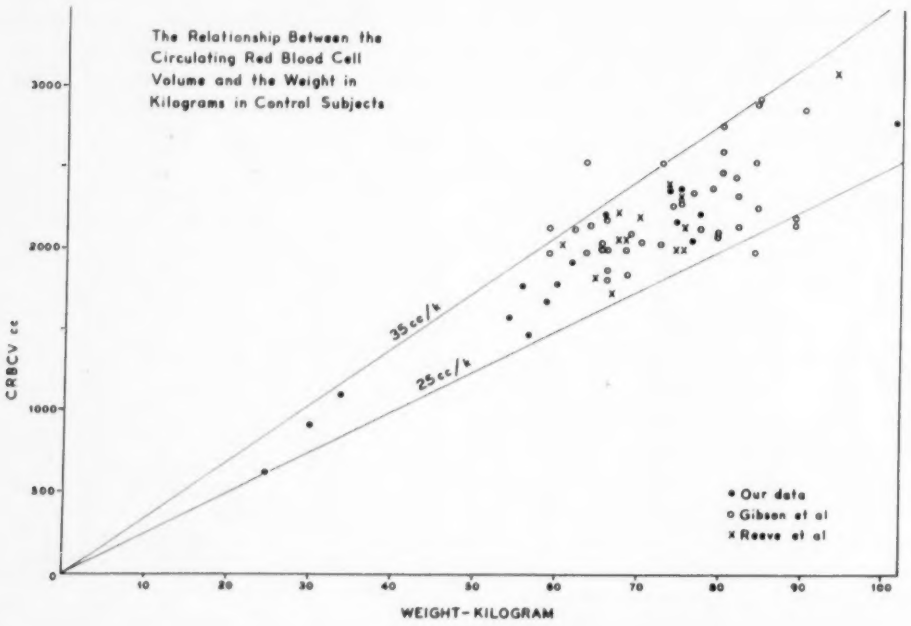

Figure 1

this reason it was used as the standard representing peripheral red blood cell values for each patient.

Normal value for the hematocrit of males at sea level is 47, with a range of 40 to 54. For females the average hematocrit has been accepted as 42, with a range of 37 to 47.[8]

Methods using isotopically tagged red blood cells for the determination of the CRBCV have been employed by numerous observers. A rather constant correlation between the CRBCV and the body weight of normal patients has been found (Fig. 1) and has been used as a practical standard of reference.[3,4,9] The validity of this correlation is supported by the work of Huff and Feller.[10] After determining the body density in a series of persons of different body configurations, they demonstrated that there was an accurate relationship between the CRBCV and the body weight in both obese and lean, normal persons. Our results in normal persons are in agreement with those of others. In patients with polycythemia vera, reported values for CRBCV are characteristically high. In the present study the values obtained are in agreement with these elevated results. It is of interest to note that in spite of therapy and a reduction of the peripheral blood hematocrit value in several instances to well within normal levels the CRBCV/kg. in these patients remained increased. It is suggested that the CRBCV/kg. is probably a more accurate guide to the effect of therapy than is the peripheral hematocrit.

In normal persons, although the range of values for CRBCV/kg. was narrow (30± 4 ml/kg.). We noted that persons with higher peripheral hematocrits did not necessarily have higher values for CRBCV/kg.

An effort was made to correlate the relationship, if any, between the peripheral hematocrit and the CRBCV/kg. In normals we found the ratio to be 1.32-1.59, with a mean of 1.47. Using data available in the literature,[3,4,9] we found this to be rather consistent (Fig. 2).

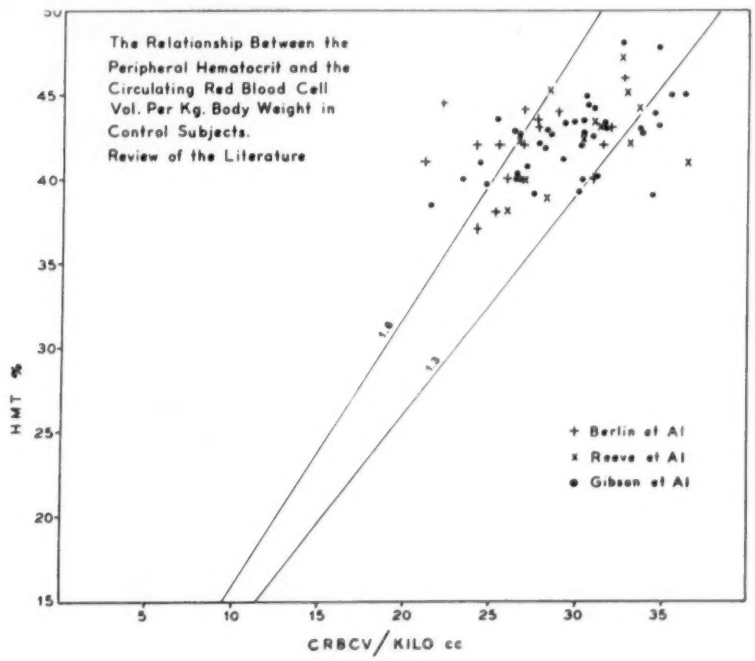

Figure 2

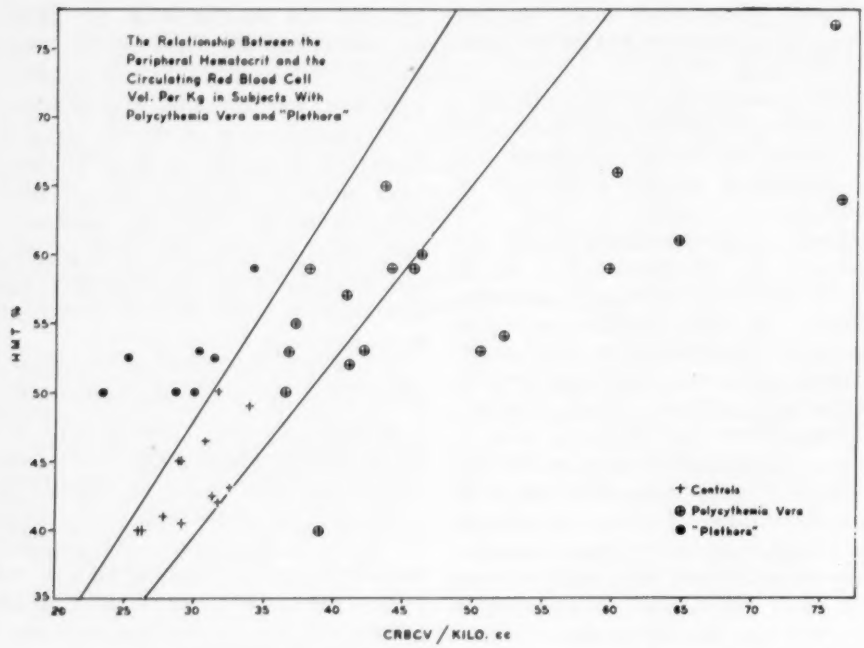
The Relationship Between the Peripheral Hematocrit and the Circulating Red Blood Cell Vol. Per Kg in Subjects With Polycythemia Vera and "Plethora"
HMT %
CRBCV / KILO. cc
+ Controls
⊕ Polycythemia Vera
● "Plethora"

Figure 3

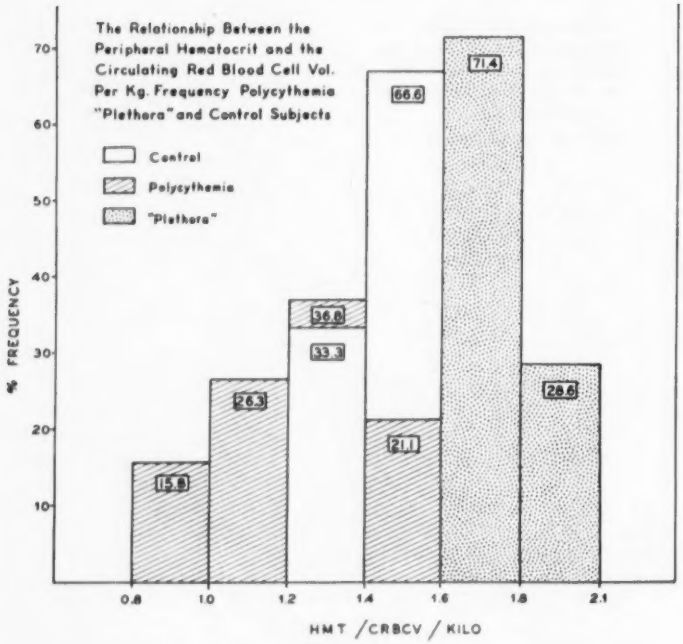

Figure 4

In polycythemia vera this ratio was markedly disturbed, with some values normal and a majority of values lower than those of the normal group. This indicates the frequency with which the hematocrit is in error (i. e., too low) as an indication of the magnitude of the circulating red blood cell volume.

In the "Plethora" group the correlation between peripheral hematocrit divided by CRBCV/kg. gave values of 1.65-2.13, with a mean of 1.82. Here the error of the hematocrit as a guide to CRBCV/kg. was on the high side (Figs. 3 and 4). There was, in fact, one patient in this group (Patient 35) with a hematocrit of 50.0 in whom the CRBCV/kg. was 23.5 ml., which is below the normal range in our series.

The concept of spurious polycythemia and anemia has been suggested previously.[11] These data support this observation and emphasize the unreliability of the peripheral hematocrit as an accurate reflection of the true hematologic status of the abnormal person.

Summary and Conclusions

The circulating red blood cell volume was determined in 12 normal persons, in 19 patients with polycythemia vera, and in 7 persons with elevated peripheral blood cell counts.

The peripheral blood values poorly reflect the total circulating red blood cell volume when corrected for body weight in patients with polycythemia vera and persons with high peripheral blood cell counts.

The ratio of the peripheral hematocrit divided by the circulating red blood cell volume per kilogram of body weight was calculated in each instance. The range of these values is defined for each group. It is suggested that this ratio is useful in indicating spurious polycythemia and spurious normalcy.

Miss Mildred Fishman and Miss Rosalie Lesser gave technical assistance.

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REFERENCES

1. Albritton, E. C., Editor: Standard Values in Blood, AF Technical Report No. 6039, Wakefield, Mass., McGregor and Werner Inc., 1952.

2. Wintrobe, M. M., Clinical Hematology, Philadelphia, Lea & Febiger, 1951.

3. Reeve, E. B., and Veall, N.: A Simplified Method for the Determination of Circulating Red-Cell Volume with Radioactive Phosphorus, Journ. Physiol., 108:12-23, 1949.

4. Berlin, N. I.; Hyde, G. M.; Parsons, R. J.; Lawrence, J. H., and Port, S.: Blood Volume of the Normal Female as Determined with P^{32} Labeled Red Blood Cells, Proc. Soc. Exper. Biol. & Med. 76:831-832, 1951.

5. Wardsworth, G. R.: The Blood Volume in Normal Women, Blood 9:1205-1207, 1954.

6. Berlin, N. I.; Hyde, G. M.; Parsons, R. J., and Lawrence, J. H.: The Blood Volume in Cancer, Cancer 8:796-802, 1955.

7. Berson, S. A., and Yalow, R. S.: The Use of K^{42} or P^{32} Labeled Erythrocytes and I^{131} Tagged Human Serum Albumin in Simultaneous Blood Volume Determinations, J. Clin. Invest. 31: 572-580, 1952.

8. Cartwright, G. E.: Diagnostic Laboratory Hematology, New York, Grune & Stratton, Inc., 1954.

9. Gibson, J. G. D.; Peacock, W. C.; Seligman, A. M., and Sack, T.: Circulating Red Cell Volume Measured Simultaneously by the Radioactive Iron and Dye Methods, J. Clin. Invest. 25:838-847, 1946.

10. Huff, R. L., and Feller, D. D.: Relation of Circulating Red Cell Volume to Body Density and Obesity, J. Clin. Invest. 35:1-10, 1956.

11. Spurious Anemia, Editorial, A.M.A. Arch. Int. Med. 90:577-579, 1952.

Renal Excretion of Phosphorus in Pseudohypoparathyroidism

Observations on the Effects of Probenecid and Acetazoleamide in Two Patients

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Pseudohypoparathyroidism, a disease first described by Albright and co-workers,[1] differs from true hypoparathyroidism in pathogenesis despite the biochemical and clinical similarities of the two conditions.[1-6] High serum phosphorus levels and low serum calcium levels are characteristic of both conditions. Hypocalcemic tetany, intracranial calcification, and cataracts may be found in both diseases (Table). While true hypoparathyroidism results from a deficiency in circulating parathyroid hormone, pseudohypoparathyroidism seems to be the result of inadequate end-organ response to parathyroid secretion.[1] Differences in response to injected parathyroid extract have been used for the differential diagnosis of the two diseases.[1,2] Despite the underlying difference in pathophysiology, the treatment of pseudohypoparathyroidism, like that of true hypoparathyroidism, has been based on the administration of either dihydrotachysterol or vitamin D and a low-phosphorus diet.[1-3] In general, the response of patients with true hypoparathyroidism has been more satisfactory.[3]

Probenecid (Benemid) has been reported to have an effect on phosphorus metabolism in both pseudo- and true hypoparathyroidism.[7] Pascale, Dubin, and Hoffman [7] observed an increase in urinary phosphorus and a decrease in serum phosphorus in a patient with pseudohypoparathyroidism and in four patients with true hypoparathyroidism during administration of this drug. No such effect has been demonstrated in euparathyroid patients.[8] This report concerns the effect of probenecid and acetazoleamide (Diamox) on two patients with pseudohypoparathyroidism. The effects of acetazoleamide were studied because, like probenecid, it affects tubular enzyme systems concerned with electrolyte resorption.[9]

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Comparison of Findings in Hypoparathyroidism and Pseudohypoparathyroidism

	Hypoparathyroidism	Pseudohypoparathyroidism
Intracranial calcifications	Common	Common
Mental deficiency	Common	Common
Cataracts	Common	Common
Subcutaneous calcifications	None	Common
Metacarpal dystrophy	None	Common
Tetany	Usual	Usual
Serum calcium	Low	Low
Serum phosphorus	Normal to high	Normal to high
Urine calcium	Normal to low	Normal to low
Urine phosphorus	Low	Low
Response to parathormone	Phosphaturia	None

Report of Cases

C. B., a 30-year-old white man, first developed episodes of tetany at the age of 22 years. He had been hospitalized on numerous occasions and treated with various regimens, including a low-phosphorus-high-calcium diet, dihydrotachysterol, large doses of vitamin D, and calcium gluconate. He responded well to therapy on each occasion, but his symptoms always recurred on discharge. An Ellsworth-Howard test performed in 1953 at another institution was reported to be consistent with the diagnosis of pseudohypoparathyroidism.

On entry to the West Side Veterans Administration Hospital, in April, 1954, the patient's main complaint was inability to maintain employment because of "nervousness." Physical examination revealed a short, round-faced man who was pleasant, loquacious, and somewhat "flighty." His skin and nails were of normal texture, and there were no subcutaneous calcifications. Chvostek's and Trousseau's signs were strongly positive. His extremities were normal except for the middle fingers, which were somewhat short (Fig. 1). No cataracts were present. His teeth were moderately carious. The remainder of the physical examination revealed no abnormalities.

The hemogram, urinalysis, and liver function tests (sulfobromophthalein, thymol turbidity, cephalin flocculation, serum bilirubin, and alkaline phosphatase) yielded normal results. The serum calcium level was 5.5 mg. per 100 cc., and the serum phosphorus, 10.5 mg. per 100 cc. The serum globulin level was consistently elevated, with values ranging from 3.0 to 4.3 gm. per 100 cc. at total protein levels varying from 6.0 to 8.3 gm. per 100 cc., respectively, during the period of observation. Study of the serum protein by filter-paper electrophoresis revealed mild elevation of the γ-globulin fraction (Fig. 2). Roentgenograms of the skull showed calcifications, presumably of the basal ganglia. The Q-T interval of the electrocardiogram was prolonged. The electroencephalogram was normal, as were the excretory urogram and roentgenograms of the long bones. Psychometric evaluation showed normal intelligence (I. Q., 100). The patient, however, was considered to have a "character disorder."

An Ellsworth-Howard test[10] was performed, using as a control a patient who had no apparent metabolic bone disease (Fig. 3). It may be seen that while the intravenous administration of 200 mg. of parathyroid extract (Eli Lilly & Company) to the patient resulted in no increase in phosphaturia, the control patient showed a twelvefold rise. There was no demonstrable change in the levels of the serum calcium and phosphorus. The lack of increase of phosphorus excretion after administration of parathyroid hormone was considered consistent with a diagnosis of pseudohypoparathyroidism.

The effects of probenecid, acetazoleamide, and dihydrotachysterol on this patient's calcium and phosphorus metabolism were studied by measurement of urinary excretion and serum levels of calcium and phosphorus (Figs. 4A and 4B). A short period of study (Fig. 4A) was followed by a period out of the hospital and then by a second, longer period of study in the hospital (Fig. 4B). During the first period of study (Fig. 4A), probenecid in a dose of 2 gm. daily was given for four days, after a control observation. This was associated with a sharp rise in the level of urinary phosphorus and of serum calcium and a sharp decrease in the serum phosphorus level.

Fig. 1.—Hands of Patient C. B., showing mild disproportion between lengths of middle and index fingers.

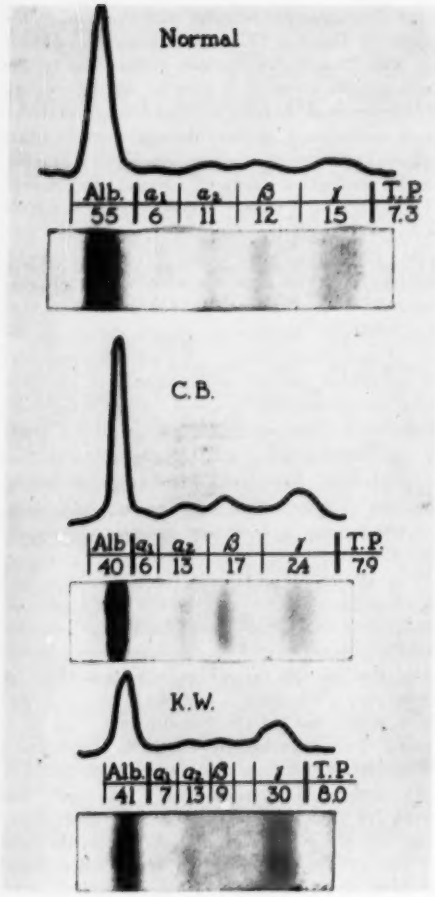

Fig. 2.—Electrophoretic patterns of normal serum and that of Patients C. B. and K. W. Please note increase in γ-globulin fraction.

After these values had returned to the pretreatment level, acetazoleamide, administered daily for four days, also resulted in an increased phosphorus excretion and a depression of the serum phosphorus levels. When control levels were again reached, after discontinuing the acetazoleamide, a dose of 3.75 mg. of dihydrotachysterol was given daily for a period of 28 days. After an initial decline, there was a slow rise in serum calcium to normal levels. There was, however, no consistent change in urinary phosphorus excretion.

After a period of five months as an outpatient, during which he received no medication, the patient was readmitted to the hospital in January, 1955, and the second set of studies was made (Fig. 4B). His serum calcium level was 6.4 mg. per 100 cc., and his serum phosphorus, 6.6 mg. per 100 cc. when readmitted. He again complained of "nervousness," and the Chvostek and Trousseau signs were again positive. No other changes in his condition were evident.

After a 4-day control period of observation, 500 mg. of acetazoleamide was given every eight hours for 25 days. On this occasion the increase in urinary phosphorus was less than had been noted during the previous period of administration of this drug. The serum phosphorus fell to lower levels, and the serum calcium rose to an average value of 8.3 mg. per 100 cc. The patient reported that he felt better. Two days after acetazoleamide was discontinued, the serum calcium fell to 6.1 mg. per 100 cc., and the patient suffered from two episodes of carpopedal spasm.

Probenecid was then readministered in a dose of 2 gm. per day. After four days the Trousseau and Chvostek signs disappeared. The serum calcium rose slightly to 7.3 mg. per 100 cc., but the urinary phosphorus excretion did not increase, and the serum phosphorus level remained unchanged. After 16 days of this therapy, the dose of pro-

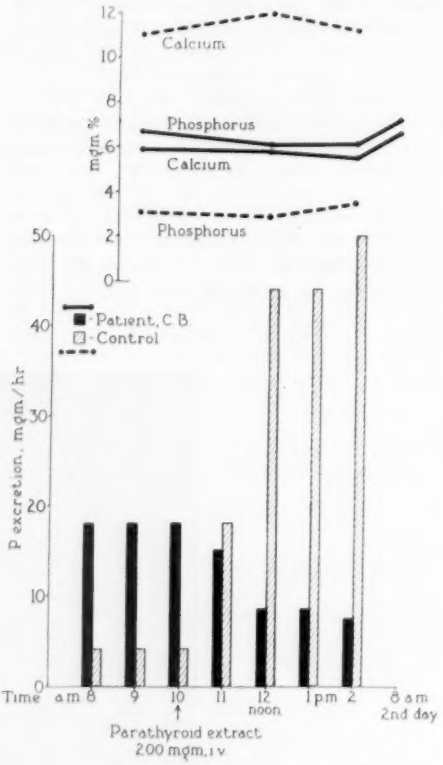

Fig. 3.—Results of Ellsworth-Howard test in Patient C. B. Please note the lack of increase in phosphaturia in contrast with the marked increase shown by the control.

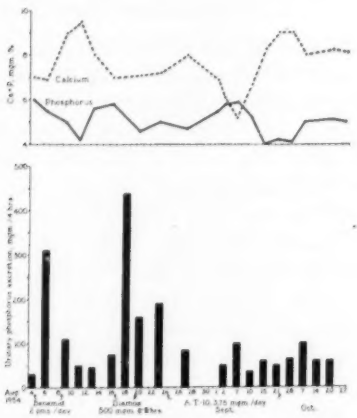

Fig. 4A.—First period of study in Patient C. B., showing the phosphaturia and associated return to normal of serum calcium and phosphorus levels induced by the administration of probenecid (Benemid). Please note of the lack of significant change of serum values during the marked phosphaturia induced by acetazoleamide (Diamox).

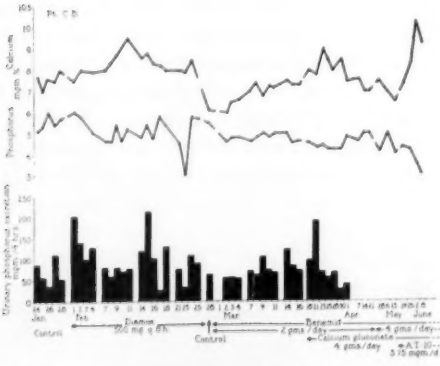

Fig. 4B.—Second period of study in Patient C. B., showing the effects of acetazoleamide (Diamox) and probenecid (Benemid) in phosphaturia to be less than demonstrated during the first study.

benecid was raised to 4 gm. per day, with a supplement of 4 gm. per day of calcium gluconate. The serum calcium rose to 9 mg. per 100 cc., but then declined gradually, so that after eight weeks of the comblined probenecid and calcium gluconate therapy the serum calcium was only 6.5 mg. per 100 cc., and the Chvostek sign had again become positive. At this time dihydrotachysterol, 3.75 mg. per day, was given in addition to the probenecid and the calcium gluconate. The patient promptly became asymptomatic. After three weeks the serum calcium was 10.5 mg. per 100 cc., and the serum phosphorus, 3.5 mg. per 100 cc. Since then, he has remained on the same therapy, and the levels of serum calcium and phosphorus have remained normal.

K. W., a 22-year-old Negro woman, has been treated at the outpatient clinic of the Research and Educational Hospitals, University of Illinois, for 10 years. There was a history of retarded physical and mental development since infancy. At the age of 6 years, right-sided major convulsions had appeared. She was treated with oral calcium at this time without effect. At the age of 13 years, she was treated with dihydrotachysterol and a high-calcium-low-phosphorus diet for one year. While there was no significant change in serum calcium and phosphorus levels, the seizures temporarily subsided, but subsequently recurred while she was still receiving dihydrotachysterol. Treatment with large doses of vitamin D was instituted, and she showed considerable improvement.

From June, 1949, until February, 1955, she received 100,000 units of vitamin D and 3 gm. of calcium lactate per day. She remained free of spasms and seizures as long as she continued this regimen. Numerous determinations between 1946 and 1955 showed serum calcium levels between 4.6 and 8.2 mg. per 100 cc. and phosphorus levels between 5.5 and 10.0 mg. per 100 cc. Skull roentgenograms in 1946 revealed calcifications of the basal ganglia. An electroencephalogram in 1952 showed multiple slow-wave foci.

The patient was admitted to the hospital for further evaluation in March, 1955. She was 137 cm. tall, weighed 73 kg. She had a peculiar round, obese, dull, childish facies. Her mental age was estimated to be 6 years. She spoke little, but was oriented as to place. Her neck and digits were unusually short, but the relative lengths of her fingers were not abnormal. Only 19 teeth were present, and all of these were malformed, with mottled enamel. There was a positive Chvostek's sign. The remainder of the physical examination revealed no abnormalities. The serum calcium level ranged from 4.4 to 5.6 mg. per 100 cc., and the serum phosphorus level, from 4.6 to 9.0 mg. per 100 cc. The serum globulin level was consistently elevated, ranging from 3.9 to 4.4 gm. per 100 cc. Study of the serum proteins by paper electrophoresis showed the γ-globulin to be elevated, comprising 28.2% of the total protein (Fig. 2). The hemogram and urinalysis were normal. Roentgenograms revealed the calcifications of the basal ganglia (Fig. 5), and calcific densities had now also appeared in the hands and thighs (Fig. 6). Prolongation of the Q-T interval consistent with the effect of hypocalcemia was present on the electrocardiogram.

Fig. 5.—Roentgenogram of skull of Patient K. W., showing calcifications in probable region of basal ganglia.

An Ellsworth-Howard Test[10] was performed on two occasions. In the first test a dose of 80 units of parathyroid extract (Eli Lilly & Company) was administered intravenously to the patient and to a control patient with subsiding pyelonephritis. No significant increase in urinary phosphorus excretion was noted in either patient. In the second test, 200 units of parathyroid extract was administered intravenously to the patient and to a different control, with chronic granulocytic leukemia. Again no significant increase in urinary phosphorus excretion was found in either patient.

The effects of probenecid and acetazoleamide on K. W. were studied. With the patient consuming a daily diet containing 830 mg. of phosphate, 2.0 gm. per day of probenecid was given for a period of six days. There was no significant change in the clinical status. A slight decrease in serum phosphorus levels observed at this time was difficult to interpret in view of the lack of significant increase in serum calcium or urinary phosphorus excretion. After an interval of two days, 0.5 gm. of acetazoleamide was administered twice daily for six days. There again was no significant effect.

The patient was discharged on 3.75 mg. of dihydrotachysterol per day but with no special dietary recommendations. During her hospital stay a consistently positive Chvostek's sign was present, but she had no major seizures. After her discharge, the family reported the recurrence of right-sided seizures.

Comment

The clinical and biochemical data of both patients were consistent with the diagnosis of pseudohypoparathyroidism. Nevertheless, there are important differences between the two cases. The man has normal intelligence, somewhat unusual in this disease. The onset of his tetany was relatively late in life. The woman is feeble-minded. In this patient symptoms secondary to hypocalcemia were early in onset. It is not known whether the mental retardation found in pseudohypoparathyroidism results from the disturbance in calcium and phosphorus metabolism or whether it results from an associated genetic defect. The physiognomy characteristic of pseudohypoparathyroidism has been found in patients without disturbed calcium and phosphorus metabolism, and the tongue-twisting term pseudo-pseudohypoparathyroidism was coined for this condition.[11]

Ellsworth and Howard,[10] in 1934, reported that parathyroid extract injected intravenously produces a greater phosphaturic effect in patients with hypoparathyroidism than in normal controls. When Albright and co-workers[1] reported the first three cases of pseudohypoparathyroidism, in 1942, they

Fig 6.—Soft-tissue calcifications in Patient K. W.

noted that no significant phosphaturia was induced by the administration of parathyroid hormone. Since then, the Ellsworth-Howard test and its modifications have been used to distinguish true hypoparathyroidism from pseudohypoparathyroidism. The lack of response of our male pseudohypoparathyroid patient to parathyroid extract in contrast to the marked phosphaturia produced in the control patient was consistent with this concept. The failure of our second patient to respond to parathyroid extract by increased phosphate excretion was also anticipated. However, the failure of the two controls in the second study to respond to parathyroid extract by increased phosphaturia made the lack of response of the patient difficult to evaluate. In 1953, however, Dent [12] reported that, in the case of certain euparathyroid patients, the administration of parathyroid extract failed to produce an increase in phosphaturia, even though increased serum calcium levels resulted. MacGregor and Whitehead [13] have made similar observations and concluded that the commercially available parathyroid extracts frequently produce little increase in renal phosphorus excretion in euparathyroid patients and may even fail to induce increased phosphaturia in true hypoparathyroid patients. Recent studies [14-16] indicate that there are at least two parathyroid hormones, one acting predominantly on bone to raise serum calcium and the other acting on the renal tubule to increase phosphorus excretion. Since the currently available parathyroid extract is standardized by the effect on serum calcium levels, it is not surprising that the effect on phosphorus may be erratic.

MacGregor and Whitehead[13] have claimed that the administration of 200 units of parathyroid extract intramuscularly for seven days will raise the serum calcium in almost every patient with true hypoparathyroidism. If the calcium is still depressed at the end of the period, a diagnosis of pseudohypoparathyroidism may be made (if the patient also has no disturbance of fat absorption to account for the hypocalcemia). This test was suggested by MacGregor and Whitehead [13] to replace the Ellsworth-Howard test for the differential diagnosis of hypoparathyroid-like disease. While it was not done on either of our patients, it deserves further evaluation. MacGregor and Whitehead [13] claim that refractoriness to parathyroid hormone in pseudohpoparathyroidism may not be complete, since, after administration of parathormone, the serum calcium may rise somewhat in some pseudohypoparathyroid patients even though normal levels are not achieved.

It is of interest that both patients had elevated serum globulin levels. Studies of serum proteins by paper electrophoresis showed increased levels of the γ-globulin fraction. The significance of this abnormality is not clear and warrants further study in other patients with pseudohypoparathyroidism.

The response of our first patient to probenecid by a marked increase in phosphorus excretion is striking and is in accord with the observations of Pascale and coworkers.[7] It may be noted in Figure 7 that, while there was an increase in urine volume during the administration of this drug, it was minimal compared to the increased phosphaturia. The greatest increase in urine volume was 50%, as compared to that of

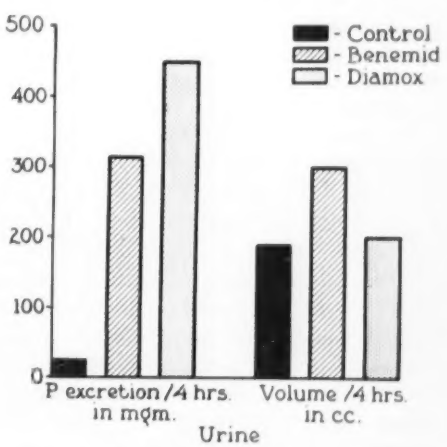

Fig. 7.—Comparison of effects of probenecid (Benemid) and acetazoleamide (Diamox) on phosphaturia and urine volume in Patient C. B., showing the mild water diuresis but marked increase in phosphorous excretion.

the control period, while phosphorus excretion increased almost 3000%. The smaller response of the first patient during the second period of administration demonstrated that a patient with pseudohypoparathyroidism who shows an initial response to probenecid may rapidly become relatively refractory. The failure of probenecid to induce significant phosphaturia in our second patient indicates that not all patients with pseudohypoparathyroidism will show even the initial response to the drug.

The distinction between the effects of probenecid and of parathyroid extract noted in this study is noteworthy. Parathyroid extract may produce phosphaturia in the normal and in the patient with true hypoparathyroidism, but not in the patient with pseudohypoparathyroidism. Probenecid, on the other hand, may increase phosphorus excretion in patients with either pseudo- or true hypoparathyroidism but does not do so in normals. The evidence suggests that probenecid and parathyroid extract differ in their mode of producing phosphorus diuresis. Although parathyroid hormone is thought to inhibit the renal tubule from resorbing phosphate, its exact physiological action is still obscure. Albright's earlier theory[17] that parathyroid hormone acts only on the renal excretion of phosphorus has been revised as the result of recent studies (cited above[14-16]). It shows the dual action of parathyroid extracts on both bone and kidneys.

Probenecid may also act by inhibiting phosphorus resorption, since there is no evidence that phosphorus is actively excreted by the tubules.[18] Tubular resorption of phosphorus can be depressed by saturation of the tubular mechanism with amino acid.[19] It has also been shown that probenecid inhibits the conjugation of amino acid with organic acids, such as benzoic acid.[20] The possible relationship between amino acid inhibition of phosphorus resorption, probenecid blockage of amino acid conjugation, and probenecid induction of phosphaturia warrants investigation. The reason for refractoriness to probenecid which developed in the first patient and which was present initially in the second patient is unclear. It is of interest that refractoriness to parathyroid extracts often develops in true hypoparathyroidism,[2] and even refractoriness to vitamin D has been reported.[21]

It should be noted that the marked phosphaturia initially produced in the first patient by acetazoleamide was also not merely the result of increased urinary output. Whether this initial effect was secondary to the production of acidosis or to a more specific action of acetazoleamide is not known. There is also no explanation for the subsequent refractoriness of the first patient and for the lack of even an initial response in the second patient to acetazoleamide.

The production of increased phosphorus excretion and even temporary clinical amelioration of a case of pseudohypoparathyroidism by probenecid and acetazoleamide is of theoretical interest. In view of the fact that this response may not be obtained in all patients and that the response, if obtained, appears to be of short duration, neither probenecid nor acetazoleamide is recommended for therapy of pseudohypoparathyroidism. Further investigation of the effect of these and related drugs in pseudohypoparathyroidism should be of interest, particularly in regard to the basic pathophysiological processes involved.

Summary

The effects of probenecid and acetazoleamide on calcium and phosphorus metabolism of two patients with pseudohypoparathyroidism are reported. One patient responded initially to each of these drugs with a markedly increased phosphaturia but subsequently became refractory to both drugs. The second patient did not respond to either drug. Possible mechanisms of the response of the first patient are discussed. Neither drug is recommended for therapy of pseudohypoparathyroidism at this time.

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REFERENCES

1. Albright, F.; Burnett, C. H.; Smith, P. H., and Parson, W.: Pseudo-Hypoparathyroidism—Example of "Seabright-Bantam Syndrome": Report of 3 Cases, Endocrinology 30:922-932, 1942.

2. Bishop, P. M. F., and de Mowbray, R. R.: Pseudohypoparathyroidism. Proc. Roy. Soc. Med. 44:952-954, 1951.

3. de Mowbray, R. R.; Smith, S. H. L., and Symonds, W. J. C.: Hypoparathyroidism and Pseudo-Hypoparathyroidism, Brit. M. J. 1:903-909, 1954.

4. Wise, B. L., and Hart, J. C.: Idiopathic Hypoparathyroidism and Pseudohypoparathyroidism: Observations on the Electroencephalogram in Hypocalcemia, A. M. A. Arch. Neurol. & Psychiat. 68:78-93, 1952.

5. Camp, J. D.: Symmetrical Calcification of Cerebral Basal Ganglia: Its Roentgenologic Significance in Diagnosis of Parathyroid Insufficiency, Radiology 49:568-577, 1947.

6. Lyle, D. J.: Ocular Syndrome of Cataract and Papilledema in Manifest Form of Parathyroid Deficiency, Am. J. Ophth. 31:580-584, 1948.

7. Pascale, L. R.; Dubin, A., and Hoffman, W. S.: Influence of Benemid on Urinary Excretion of Phosphate in Hypoparathyroidism, Metabolism 3:462-470, 1954.

8. Spurr, C. L.; Ford, R. V., and Moyer, J. H.: The Effect of Probenecid (Benemid) on Phosphate Excretion and Other Metabolic Processes, Am. J. M. Sc. 228:256-261, 1954.

9. Nadell, J.: The Effects of the Carbonic Anhydrase Inhibitor "6063" on Electrolytes and Acid-Base Balance in 2 Normal Subjects and 2 Patients with Respiratory Acidosis, J. Clin. Invest. 32:622-629, 1953.

10. Ellsworth R., and Howard, J. E.: Studies on Physiology of Parathyroid Glands: Some Responses of Normal Human Kidneys and Blood to Intravenous Parathyroid Extract, Bull. Johns Hopkins Hosp. 55:296-308, 1934.

11. Miles, J., and Elrick, H.: Pseudo-Pseudohypoparathyroidism: Report of a New Case, J. Clin. Endocrinol. 15:576-584, 1955.

12. Dent, C. E.; Bishop, P. M. F., and de Mowbray, R. R.: Discussion on Physiology and Clinical Disorders of the Parathyroid Glands, Proc. Roy. Soc. Med. 46:291, 1953.

13. MacGregor, M. E., and Whitehead, T. P.: Pseudo-Hypoparathyroidism: A Description of 3 Cases and a Critical Appraisal of Earlier Accounts of the Disease, Arch. Dis. Childhood 29: 398-418, 1954.

14. Munson, P. L.; Kenny, A. D., and Iseri, O. A.: Biological Assay of Calcium-Mobolizing Hormone (CMH) Based on Maintenance of Serum Calcium in Parathyroidectomized Rats, Fed. Proc. 12:249, 1953.

15. Kenny, A. D.; Vine, B. G., and Munson, P. L.: Estimation of Ratio of Phosphaturic and Calcium-Mobilizing Activities in Parathyroid Extracts, Fed. Proc. 13:241, 1954.

16. Grollman, A.: The Role of the Kidney in the Parathyroid Control of the Blood Calcium as Determined by Studies on the Nephrectomized Dog, Endocrinology 55:166-172, 1954.

17. Albright, F.: Metabolic Effects of A. T. 10 Compared with Those of Vitamin D and with Those of Parathyroid Hormone, Tr. A. Am. Physicians 53:221-226, 1938.

18. Smith, H. W.: The Kidney: Structure and Function in Health and Disease, New York, Oxford University Press, 1951, p. 114.

19. Ayer, J. L.; Schiess, W. A., and Pitts, R. F.: Independence of Phosphate Reabsorption and Glomerular Filtration in the Dog, Am. J. Physiol. 151:168-173, 1947.

20. Beyer, K. H.; Wiebelhaus, V. D.; Tillson, E. K.; Russo, H. F., and Wilhoyte, K. M.: Benemid, P-(di-n-propylsulfamyl)-benzoic acid. Inhibition of glycine conjugative reactions, Proc. Soc. Exper. Biol. & Med. 74:772, 1950.

21. Dent, C. E.; Harper, C. M.; Morgans, M. E., and Philpot, G. R.: Insensitivity to Vitamin D Developing During the Treatment of Postoperative Tetany: Its Specificity as Regards the Form of Vitamin D Taken, Lancet 2:687-690, 1955.

Carbohydrate Metabolism in Brain Disease

VII. The Effect of Glutathione on Carbohydrate Intermediary Metabolism in Schizophrenic and Manic-Depressive Psychoses

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Patients with schizophrenic, manic-depressive, and involutional psychoses have a disorder of carbohydrate metabolism; the origin of this disorder is as yet unknown.[1] However, it is known that it is not due to hepatic dysfunction,[2] that it is not remedied by thiamine, and that it disappears only with remission of the psychoses, regardless of how remission has come about. It also is known that patients with these psychoses commonly have blood glutathione levels that are in or below the lower range of normal.[3] Glutathione is an important coenzyme in several metabolic processes, and it also may have other functions in intermediary metabolism; at any rate, observations in man[4] indicate that it accelerates carbohydrate utilization. In view of these facts, it was decided to study the effects of the administration of glutathione on the carbohydrate metabolism of patients with the above-mentioned psychoses.

Material and Methods

Five patients were studied. Four were men with depressions; their ages ranged from 54 to 73 years. The fifth subject was a 26-year-old woman with chronic schizophrenia.

The blood chemical methods used were those previously described.[1,4] A glucose-tolerance test[1] was made in each case on the day before glutathione administration was started; 100 gm. of glucose was used in each instance. The test was repeated on the first or second day following the last infusion of glutathione. The patients were given a high-carbohydrate diet for several days before each test.

Glutathione was given in doses of 0.5 gm. per kilogram of body weight, i. e., 30 to 50 gm. per infusion. The glutathione was dissolved in a liter of isotonic sodium chloride solution and was given intravenously in two to five hours. When given in less than two hours it sometimes caused hypotension; when given in two to three hours it caused nasal stuffiness in some instances and nosebleeds in two patients. The stuffiness disappeared when the rate of infusion was slowed somewhat; the nosebleeds did not occur when the infusion was given at the slowest rate. The schedule of infusions and the total amounts given varied from patient to patient (Table 1).

TABLE 1.—*Schedule of Infusions and Amounts*

Case	No. of Infusions	Total No. Elapsed Days	Total Dose, Gm./Kg.	Average Daily Dose, Gm./Kg.
1	6	9	3	0.33
2	8	17	4	0.24
3	7	9	3.5	0.39
4	13	15	6.5	0.43
5	11	12	5.5	0.46

Observations

CASE 1.—Man, age 54. Diagnosis: psychoneurotic disorder; depressive reaction. The history was one of depression and insomnia for about five months. Past history revealed a concussion of the brain 20 years previously. Examination was not remarkable except for a blood pressure of 180/110. The patient was given six infusions of glutathione over a period of nine days. The blood glutathione concentration was 44 mg. per 100 ml. of erythrocytes before treatment and 48 mg. after treatment. Before treatment, oral administration of glucose caused an abnormal rise in blood glucose, lactate, pyruvate, and α-ketoglutarate levels.

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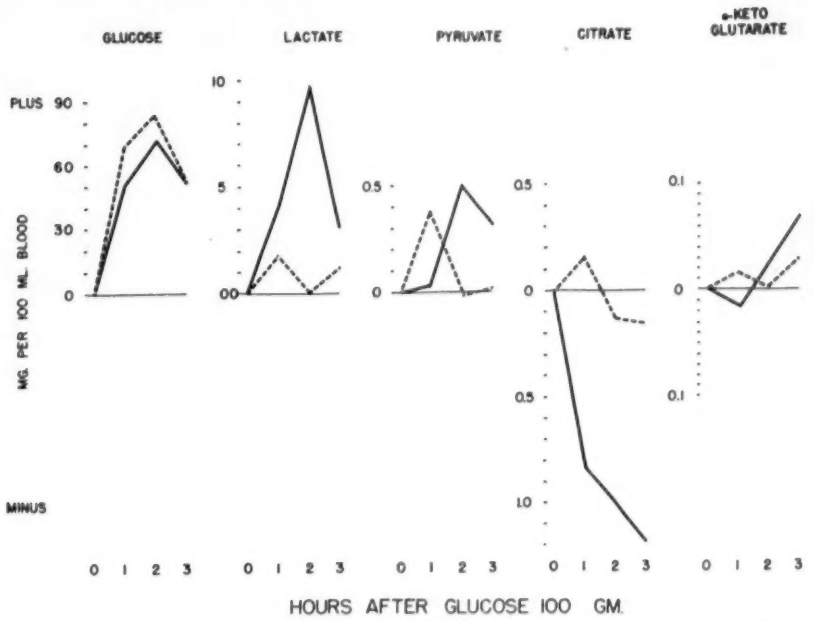

Fig. 1.—Effect of glutathione in Case 1. Solid lines show changes in blood constituents caused by 100 gm. of glucose before giving glutathione; broken lines show corresponding changes after a course of glutathione.

Two days after the last of the infusions a second test showed that the curves for lactate, pyruvate, and α-ketoglutarate were improved; however, only the first was completely normal. The curve for glucose was unchanged, and that for citrate, initially normal, was still within normal limits but was different in shape. No clinical improvement was noted (Fig. 1).

CASE 2.—Man, age 73. Diagnosis: manic-depressive psychosis, depressed phase. The history was one of severe anxiety, insomnia, and depression for about six months, with poor therapeutic responses to electroshock, chlorpromazine, and testosterone. The patient had had three previous depressions, the first one having occurred 32 years previously. The family history revealed psychotic depressions in the patient's father, grandfather, and paternal uncle and in three (of four) brothers. The past history included pneumonia, followed by hemolytic anemia caused by sulfonamides, 12 years previously; varicose veins; nocturia, and constipation. Physical examination was not remarkable except for cardiac enlargement, an apical systolic murmur, an enlarged prostate gland, and a blood pressure of 188/100. The patient was given four infusions of glutathione over a six-day period; after a lapse of five days he was given four more infusions over a seven-day period. His blood glutathione concentration was 44 mg. per 100 ml. of erythrocytes before treatment and 42 mg. after treatment. Before treatment, administration of glucose caused abnormal rises in blood glucose, lactate, pyruvate, and α-ketoglutarate levels. After treatment a second test showed no change in the blood glucose, lactate, or citrate curves. The curve for pyruvate was more nearly normal; that for α-ketoglutarate was completely so (Fig. 2). The patient's only clinical change consisted in a feeling of relaxation; his depression was not diminished.

CASE 3.—Man, age 67. Diagnosis: manic-depressive psychosis, depressed phase. The history was one of depression, confusion, and indecision of four months' duration, with a poor response to electroshock therapy received one month after the onset. The patient had had a depression 10 years previously, but on that occasion the condition had improved greatly after shock therapy. His history also revealed a good deal of dental trouble, a herniorrhaphy 11 years before admission, and nocturia. Examination was not remarkable except for varicose veins and a blood pressure of 180/110. The patient was given seven infusions of glutathione in nine days. Before treatment his blood glutathione concentration ranged between 29 and 36 (average 33) mg. per 100 ml. of erythrocytes; after treatment it ranged between 46 and 48 (average 47) mg. Administration of glucose before treatment revealed abnormal curves for blood glucose, lactate, pyruvate, citrate, and α-

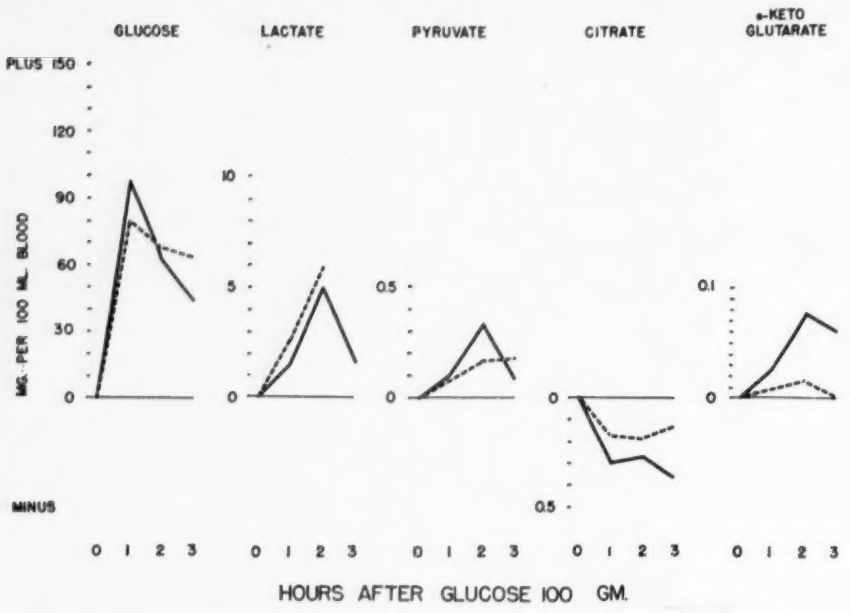

Fig. 2.—Effect of glutathione in Case 2. Solid lines show changes in blood constituents caused by 100 gm. of glucose before giving glutathione; broken lines show corresponding changes after a course of glutathione.

ketoglutarate. After treatment a second test showed that all curves except that for glucose were normal. The patient showed clinical improvement after the treatments and was discharged a few weeks later.

Case 4.—Man, age 54. Diagnosis: manic-depressive psychosis, depressed phase. The history was one of four months of confusion, depression, and irritability. The patient had had three such episodes previously (all four had begun in the late winter); electroshock treatment had been effective at these times. The past history was otherwise not remarkable. Physical examination revealed moderate emphysema, slight cardiac hypertrophy, and a blood pressure of 140/100. The patient was given 13 infusions of glutathione over a period of 15 days. His blood glutathione level was between 27 and 34 (average 30) mg. per 100 ml. of erythrocytes before treatment and 53 mg. after treatment. Administration of glucose before treatment revealed abnormal curves for blood glucose, lactate, pyruvate, and citrate; administration of glucose after treatment revealed improvement in all these curves, all but that for glucose now being completely normal. The curve for blood α-ketoglutarate was normal before and after treatment (Fig. 4). The patient was clinically improved, but several weeks later he relapsed and was given electroshock. He made an excellent recovery, but this lasted for only a few months.

Case 5.—Woman, age 26. Diagnosis: schizophrenia, paranoid type. The illness had begun two and one-half years previously and, except for slight or moderate partial remissions associated with insulin therapy, was a chronic one. The family history revealed that one of four siblings had a chronic paranoid psychosis. Past history was not remarkable except for obesity during adolescence and an appendectomy during the patient's early twenties. At the time of the present studies the patient was vague, apathetic, and occasionally silly. She ate poorly and spent much of her time huddled against a wall, talking only to one or two persons and communicating with any others only in unintelligible gestures. She was given 11 infusions of glutathione in 12 days. Her blood glutathione level was 38 mg. per 100 ml. of erythrocytes before treatment and 50 mg. after the last infusion. Administration of glucose before treatment showed abnormal curves for all blood carbohydrate constituents measured. After treatment this test showed improvement in all the curves except that for citrate; however, the fasting levels for plasma citric acid were almost 1 mg. lower after treatment than before it. The patient was clinically improved. She became sociable and showed interest in reading (she claimed that her mind was now clear enough so that she could understand what she read); she was no longer

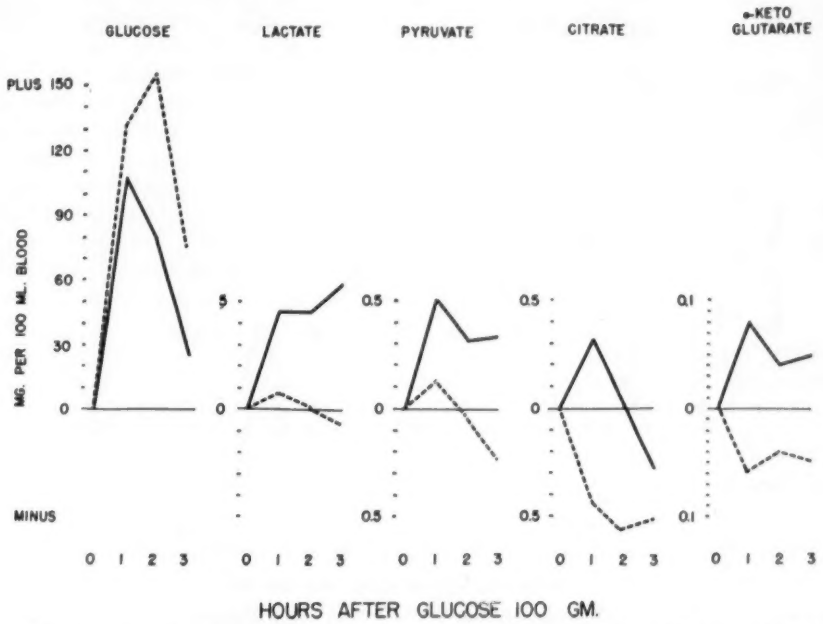

Fig. 3.—Effect of glutathione in Case 3. Solid lines show changes in blood constituents caused by 100 gm. of glucose before giving glutathione; broken lines show corresponding changes after a course of glutathione.

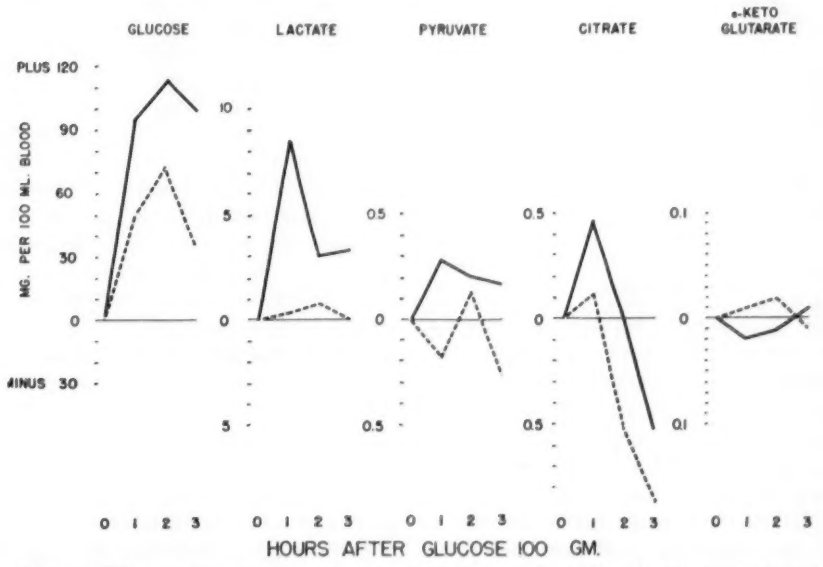

Fig. 4.—Effect of glutathione in Case 4. Solid lines show changes in blood constituents caused by 100 gm. of glucose before giving glutathione; broken lines show corresponding changes after a course of glutathione.

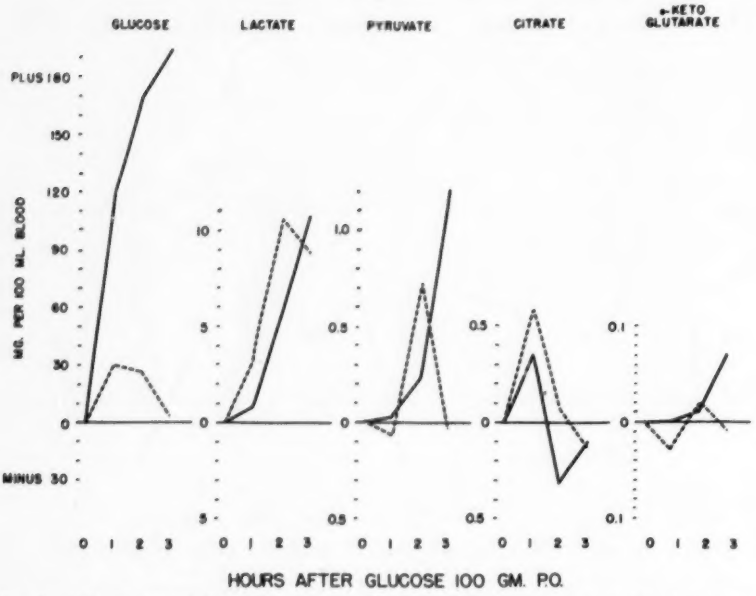

Fig. 5.—Effect of glutathione in Case 5. Solid lines show changes in blood constituents caused by 100 gm. of glucose before giving glutathione; broken lines show corresponding changes after a course of glutathione.

TABLE 2.—*Fasting Values of Blood Constituents Before and After Glutathione*

Case	Glucose, Mg./100 Ml.		Lactate, Mg./100 Ml.		Pyruvate, Mg./100 Ml.		Citrate, Mg./100 Ml.		α-Keto Glutarate	
	Before	After	Before	After	Before	After	Before	After	Before	After
1	70	76	7.5	11.5	1.02	1.13	1.90	1.45	0.14	0.15
2	66	73	6.5	8.5	0.62	0.68	1.40	1.54	0.24	0.20
3	120	105	5.8	10.5	0.52	0.94	1.80	2.00	0.09	0.16
4	88	70	7.3	7.8	0.80	0.97	2.40	2.40	0.14	0.12
5	52	60	10.5	9.5	1.04	1.18	2.85	1.94	0.14	0.14
Averages	79	77	7.5	9.6	0.80	0.98	2.07	1.87	0.17	0.15

mute, and she ate fairly well. However, this improvement was maintained for less than a week after the last infusion.

Comment

The data show that administration of large amounts of glutathione caused improvement in carbohydrate intermediary metabolism in all subjects of the present study. The most striking changes involved the utilization of ketoacids: In all five instances the curves for pyruvic acid improved, becoming more nearly normal in three and completely so in two; the curves for α-ketoglutaric acid became normal in four of the five subjects, the fifth having been normal before treatment. The curves for lactate (which presumably is in equilibrium with pyruvate) were improved in four of the five subjects also. On the other hand, the curves for blood citrate were improved in only two of the five; however, two of the remaining three had been normal before treatment. All five glucose curves were abnormal before treatment, and only one became normal after treatment. These evidences of improvement of intermediary metabolism are consistent with observations previously made in this laboratory.[4]

The clinical improvement that was noted in the four patients who received the largest amounts of glutathione was either too slight

or too transitory to suggest that glutathione by itself is therapeutically useful. The nature of the metabolic change that led to biochemical (and also clinical) improvement cannot be stated. It is known that glutathione in vitro counteracts the effects of some hallucinogenic agents,[6] but it is hardly likely that this fact can account for the substance's effect in these patients. Ant [6] reported that he gave 50 mg. of glutathione to each of 45 depressed patients and observed relief of many of their symptoms; it is probable, however, that his results were due to some other aspect of his treatment.

The mechanisms of the changes here reported are not shown. The blood glutathione level remained elevated for two weeks or more after the infusions. However, in one patient both biochemical and clinical relapse occurred within a week after the last infusion. Of course only the blood levels could be measured, and no information could be obtained about possible changes in the tissue concentrations.

Some of the untoward effects of the infusions are of interest. The hypotension and bradycardia that accompanied infusions given too rapidly might have been due to the fact that the glutathione combined with the inactivated epinephrine and arterenol; organic sulfides have this property.[7] The nosebleeds that occurred suggest impairment of clotting mechanisms; the sulfhydryl radical is known to interfere with clotting.[8] However, when a slow rate of infusion was maintained, none of these untoward effects was observed.

Summary and Conclusions

The disorder of carbohydrate intermediary metabolism that is regularly found in patients with schizophrenic, manic-depressive, and involutional psychoses was largely reversed in five patients who were given glutathione in very large amounts. In this connection the chief effect of glutathione seems to be to accelerate the utilization of ketoacids.

Certain avoidable untoward effects of the administration of glutathione are discussed.

McLean Hospital.

REFERENCES

1. Henneman, D. H.; Altschule, M. D., and Goncz, R. M.; Carbohydrate Metabolism in Brain Disease: II. Glucose Metabolism in Schizophrenic, Manic-Depressive, and Involutional Psychoses, A. M. A. Arch. Int. Med. 94:402, 1954.

2. Henneman, D. H.; Altschule, M. D., and Goncz, R. M.: Carbohydrate Metabolism in Brain Disease: III. Fructose Metabolism in Schizophrenic, Manic-Depressive, and Involutional Psychoses, A. M. A. Arch. Neurol. & Psychiat. 72: 696, 1954.

3. Altschule, M. D.; Siegel, E. P., and Henneman, D. H.: Blood Glutathione Level in Mental Disease Before and After Treatment, A. M. A. Arch. Neurol. & Psychiat. 67:64, 1952.

4. Henneman, D. H.; Altschule, M. D., and Goncz, R. M.: Effect of Intravenous Administration of Glutathione in Man on Blood Glucose, Some Other Blood Carbohydrates and Serum Inorganic Phosphate, Metabolism 4:433, 1955.

5. Randall, L. O.: The Inhibition of the Anaerobic Glycolysis of Rat Brain by Adrenochrome, J. Biol. Chem. 165:733, 1946.

6. Ant, M.: The Nutritional Factor in Depressive States, Am. J. Digest. Dis. 21:261, 1954.

7. Schroeder, H. A.; Menhard, E. M., and Perry, H. M., Jr.: The Antihypertensive Properties of Some Mercaptans and Other Sulfur-Containing Compounds, J. Lab. & Clin. Med. 45: 431, 1955.

8. Carter, J. C., and Warner, E. D.: Evaluation of Disulfide Bonds and Sulfhydryl Groups in the Blood Clotting Mechanism, Am. J. Physiol. 179:549, 1954.

Carbohydrate Metabolism in Brain Disease

VIII. Carbohydrate Metabolism in Wernicke's Encephalopathy Associated with Alcoholism

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Introduction

Wernicke's encephalopathy is a consistent and readily recognized clinical syndrome, the central feature of which is an acute ocular disturbance. This disturbance takes the form of horizontal and vertical nystagmus and various degrees of paralysis of conjugate gaze and of the external recti muscles. In nearly all cases there are also mental symptoms and ataxia, the latter symptom mainly affecting the patient's stance and gait. In the acute stage of the illness the dominant mental manifestations are a general lack of interest and of attentiveness, together with apathy and occasionally drowsiness. Spontaneous speech is minimal, but disorientation is easily demonstrated. In some instances it is obvious at the outset that the patient has a dementia that is ordinarily regarded as Korsakoff's psychosis, that is, one which comprises impairment of recent memory and inability to retain and recall newly presented material. Usually, however, the features of the Korsakoff psychosis become prominent only after dietary therapy has been instituted.

The pathologic changes are mainly in the brain stem; they involve the mammillary bodies and the regions adjacent to the aqueduct and to the third and fourth ventricles. The lesions are characterized by various degrees of necrosis of both nerve cells and nerve fibers, together with reactive changes of microglia and astrocytes, alteration of the small blood vessels, and, in some instances, petechial hemorrhages.

Although in this country the syndrome is almost entirely limited to alcoholics, it is now established that nutritional deficiency is the cause.[1-3] The specific nutritional lack underlying most, if not all of the symptoms, is that of thiamine.[4-7] Under controlled dietary conditions thiamine alone induces clearing of ophthalmoplegia within a few hours of its administration. Nystagmus and ataxia also improve under this regimen, but more slowly and at times incompletely. The response of the mental symptoms to thiamine is more difficult to define. In terms of increased alertness, cheerfulness, attentiveness, and ability to concentrate and to sustain a conversation, thiamine alone has a rapidly beneficial effect; with respect to memory defect and the ability to retain and recall newly presented material, the effect of thiamine is still debatable.[6,8]

Wernicke's syndrome is also characterized by an abnormality of carbohydrate metabolism, more specifically by an accumulation of pyruvic acid in the blood.[13] It has long been known that the same abnormality occurs in beri-beri and experimental vitamin B_1 deficiency[9,10]; it has been well established, in these diseases, that the defect consists in impaired oxidation of pyruvic acid, which is formed during the breakdown of glucose.[11] This biochemical abnormality is

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explained by the fact that vitamin B_1 pyrophosphate functions as a coenzyme in this oxidative process.[12]

Earlier workers showed that fasting blood pyruvate levels are elevated in patients with Wernicke's syndrome[13]; they showed also that in response to a "glucose load," i. e., a large intake of glucose, the blood pyruvic acid rose to higher levels than normal, and that these high levels were maintained for abnormally long periods. These defects could be corrected by the administration of thiamine or of vitamin B complex. There is still a need, however, for more precise information relating the abnormal pyruvate metabolism of thiamine deficiency alone to the individual symptoms of disease. This is especially important because patients with some central nervous system diseases that are not caused by starvation or vitamin deficiency exhibit disorders of intermediary carbohydrate metabolism.[14-16]

The present studies were undertaken to obtain information concerning (*a*) the intermediary carbohydrate metabolism in a brain disease caused by a vitamin deficiency, (*b*) the effect of administered thiamine on the disease and on its associated metabolic disturbance, and (*c*) the validity of the concept that thiamine deficiency may be evaluated on the basis of changes in pyruvate metabolism.

Materials and Methods

Part I

Twelve patients with Wernicke's syndrome were the subjects; they included nine men and three women, ranging in age from 31 to 66 years. Only patients who had definite ophthalmoplegia and had received no food after admission to the hospital were included in the study. All the patients, with one exception, had the characteristic mental symptoms. Histories obtained from friends and relatives in each case proved that the patients were chronic alcoholics and that their diet had been grossly inadequate for months before admission. All the patients showed evidence of loss of weight and muscle bulk. None showed jaundice, ascites, or esophageal bleeding, but all but two had an enlarged liver and/or abnormal "liver function" tests. In three patients the tongue was red and depapillated, and one showed the signs of retrobulbar neuropathy. Knee and ankle jerks were absent in 8 of the 12 patients, but there were no other signs of peripheral neuropathy. None of the patients suffered from other serious bodily diseases or from obvious cardiac beri-beri, and none had any fever.

From the time of admission to the hospital, the patients received only a rice diet,* which was

Calories	2001		Iron	8	mg.
Protein	12	gm.	Vitamin A	2200	i.u.
Fat	1	gm.	Ascorbic acid	115	mg.
Carbohydrate	486	gm.	Thiamin	0.4	mg.
Calcium	0.2	gm.	Riboflavin	0.3	mg.
Phosphorous	0.4	gm.	Niacin	5	mg.

maintained for the duration of the experiment (up to 10 days). This regimen supplied the patient with about 2000 Cal. daily but was deficient in the B-vitamins. The rice diet was given alone for one or two days and thereafter was continued, but with the addition of crystalline thiamine in therapeutic doses. With the rice diet alone no improvement was observed in any of the neurologic signs, although the period of observation was too brief to be certain of this, being only 24 hours in nine patients and 48 hours in three others. After the observation period and before thiamine was begun, blood was drawn for pyruvate and lactate estimation. This was done in the morning, the patient being in the fasting state and having been confined to bed since his admission to the hospital. Fifty milligrams of 50% dextrose was then administered intravenously over a period of five to eight minutes. Thirty minutes after the termination of the dextrose injection samples of blood were again drawn for pyruvate and lactate estimation. After this, the patient was given 100 mg. of thiamine intramuscularly. This dose was given daily in addition to the rice diet, and observations were made on the blood pyruvate and lactate levels once or twice again in each patient, at intervals varying from one to nine days.

In this portion of the study the blood lactic acid concentration was measured by the method of Barker and Summerson[17]; the blood pyruvic acid level was measured by the method of Friedemann and Haugen[18] (This method includes α-ketoglutaric acid in the determination.)

Pyruvic and lactic acid concentrations in the blood were also estimated in 17 adult patients who served as controls. These estimations were made both in the fasting state and one-half hour after the injection of dextrose, as described above. The control patients were selected from the neurological ward of the Massachusetts General

* This diet is the one used by Dr. Walter Kempner, of Duke University. It consists of rice, fruit, fruit juices, and sugar or honey, and contains the following nutrients:

Hospital. Most of them were convalescing from minor diagnostic or surgical procedures; none suffered from malnutrition, diabetes, or recognizable disease of the central or peripheral nervous system.

Part II

Five patients, ranging in age from 41 to 65 years, were studied. Four were men. The clinical characteristics of this group were similar to the first. All the patients were alcoholics of long standing and showed obvious signs of malnutrition. Only one was free of mental symptoms. In four patients the liver was slightly enlarged and "liver function" tests were abnormal. Three of the five patients showed absence of ankle jerks, but this was the only evidence of neuropathy.

The experimental procedure was similar to that described in Part I, with the following exceptions: Immediately on admission to the hospital the patients were placed on a rice diet (as shown in footnote to Part I). On the days on which the patients failed to eat all that was given to them, they received a supplement of 1500 cc. of 10% glucose in water. Four patients were maintained on this regimen for three full days before the studies of carbohydrate metabolism were undertaken; the fifth patient was tested after two days of the experimental diet.

In this part of the study 50 gm. of dextrose was given intravenously in two hours, and blood glucose and lactic, pyruvic, citric, and α-ketoglutaric acid concentrations were measured as previously described[9]; the pyruvic and α-ketoglutaric acids were measured separately. Although fasting values were obtained in all five cases, satisfactory dextrose tolerance tests could be carried out in only three.

Observations

Part I

A. Control Values.—The fasting pyruvic acid concentrations ranged from 0.8 to 1.5 mg. per 100 ml. of blood; the average was 1.3. The fasting lactic acid concentrations ranged from 4.7 to 12 mg. per 100 ml. of blood; the average was 6.4. One-half hour after the completion of the dextrose injections, the values for pyruvic acid ranged from 1.2 to 1.9 mg. per 100 ml. of blood, with an average of 1.5; for lactic acid the range was from 6.1 to 12.1 mg. per 100 ml. of blood, with an average of 8.5.

B. Observations in Wernicke's Syndrome.—Fasting Values[1] Before Treatment with Thiamine: The fasting pyruvic acid concentrations ranged from 0.8 to 3.6 mg. per 100 ml. of blood; the average was 2.6. With one exception, all the patients had fasting values above 1.5 mg. per 100 ml. of blood, the upper limit of our normal range (Table 1 and Fig. 1).

Fasting values for blood lactic acid concentration ranged from 4.0 to 20.6 per 100 ml. of blood; the average was 12.1 (Table 1).

Fasting Values[2] After Treatment with Thiamine: After thiamine alone was added to the B-deficient diet, there was a decrease in the fasting levels of pyruvate in all except one patient, in whom the level was normal to begin with. In four patients the measurements were repeated within 24 hours after the administration of thiamine; in all four there was a decrease in the blood pyruvate level in this period of time, although it had returned to normal levels in only one. In another case the blood pyruvate values returned to normal within 48 hours, and in three other cases within 72 hours (Table 1 and Fig. 1).

TABLE 1.—*Effects of Thiamine and Blood Pyruvic and Lactic Acids in the Fasting State and After Administration of Dextrose*

Case No.	Date	Pyruvic Acid, Mg./100 Cc.		Lactic Acid, Mg./100 Cc.	
		Fasting	½ Hr. After Dextrose	Fasting	½ Hr. After Dextrose
1	6/30/53*	2.4	3.1	15	16
	7/3/53	1.9	2.1	9.9	11.2
	7/7/53	1.0	1.2	8	10.3
2	7/1/53*	2.8		18.5	
	7/2/53	1.1		6.1	
3	8/4/53*	2.9	3.8	10.8	13.6
	8/5/53	2.0	2.7	6.8	9.1
	8/7/53	1.3	2.7	12.8	16.4
4	8/13/53*	0.8	1.2	20.6	12.8
	8/14/53	0.9	1.8	7.5	22.6
	8/22/53	0.3	0.5	20.6	22.6
5	11/6/53*	2.1	2.0	9.3	8.1
	11/10/53	0.8	0.9	6.9	6.3
6	11/18/53*	2.7	2.6	8.3	8.5
	11/20/53	1.2	1.4	3.5	6.4
	11/24/53	1.5	1.4	5.2	6.6
7	11/24/53*	3.0		8.1	
	11/27/53	1.5	1.9	5.2	10.2
	12/1/53	1.6	2.5	8.8	15.6
8	12/3/53*	2.6	3.3	16.4	18.2
	12/4/53	1.6	2.0	8.1	12.1
	12/8/53	1.2	1.7	8.5	9.3
9	12/21/53*	1.6	2.1	4.0	8.1
	12/31/53	1.2	1.8	11.2	11.2
10	12/22/53*	2.5	2.9	11.2	17.6
	12/23/53	1.6	2.0	7.3	9.1
11	2/24/54*	3.6	4.0	11.6	18.5
	3/1/54	1.2	1.4	12.3	21.8
12	2/26/54*	1.9	1.9	11.8	11.9
	3/1/54	1.2	1.8	8.5	16.5

*Before thiamine.

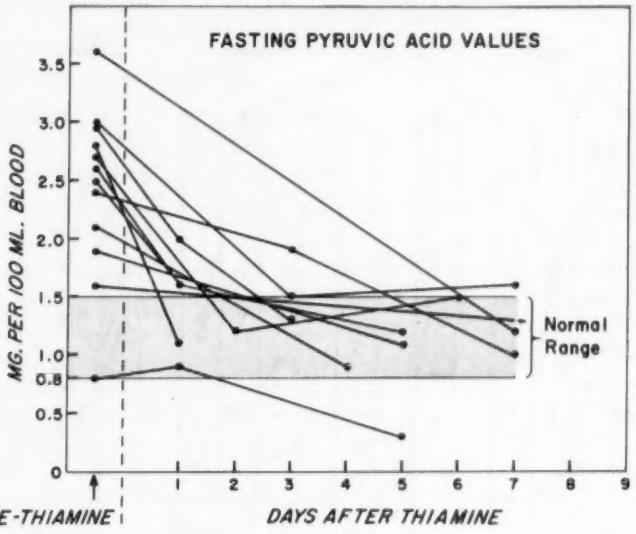

Fig. 1.—Fasting pyruvic acid values before and after treatment with thiamine (Part 1, method of Friedemann and Haugen). The shaded area indicates the range of normal values.

The changes in blood lactic acid concentration after administration of thiamine were irregular; the values after thiamine therapy were as frequently unchanged as they were lowered (Table 1).

The ratio between the fasting blood pyruvate and lactate concentrations fell on nine occasions, rose on six, and was unchanged on one after treatment with thiamine.

Changes After Intravenous Injection of Dextrose[1] Before Treatment with Thiamine: In 10 patients so studied, blood pyruvic acid levels rose after administration of dextrose in 7; the concentration fell in 2 and was unchanged in 1. One-half hour after the infusion of dextrose the blood pyruvate concentration ranged between 1.2 and 4.0 mg. per 100 ml. of blood; the average was 2.7 (Table 1). Of the 10 patients so studied, all but two showed values above the upper limit of normal; of the 2 patients who showed normal values after receiving dextrose, one had an abnormal fasting level (Table 1). The blood lactate level rose in eight patients and fell in two (Table 1).

The ratio between blood pyruvate and lactate concentrations after administration of dextrose was higher than in the fasting state in four patients, lower in five, and the same in one.

Changes After Intravenous Injection of Dextrose[2] After Treatment with Thiamine: The blood pyruvate level rose after the administration of dextrose in 16 of 17 experiments; the rise was to abnormal levels in 6 experiments in 5 subjects (Table 1). The amount of rise in blood pyruvate concentration following the administration of detrose was less after treatment with thiamine than before in only 8 of 15 experiments; it was the same in 1 and greater in 6 (Table 1).

The ratio between blood pyruvate and lactate concentrations after the administration of dextrose was lower after than before treatment with thiamine in 13 of 15 experiments; it was unchanged in 1 and higher in 1.

Part II

A. Fasting Blood Concentrations.—Fasting blood glucose concentrations were initially slightly elevated in all patients and fell to normal after thiamine was added to the regimen, except in one patient who died unexpectedly. No further change occurred in the surviving patients after they were given a full diet (Fig. 2).

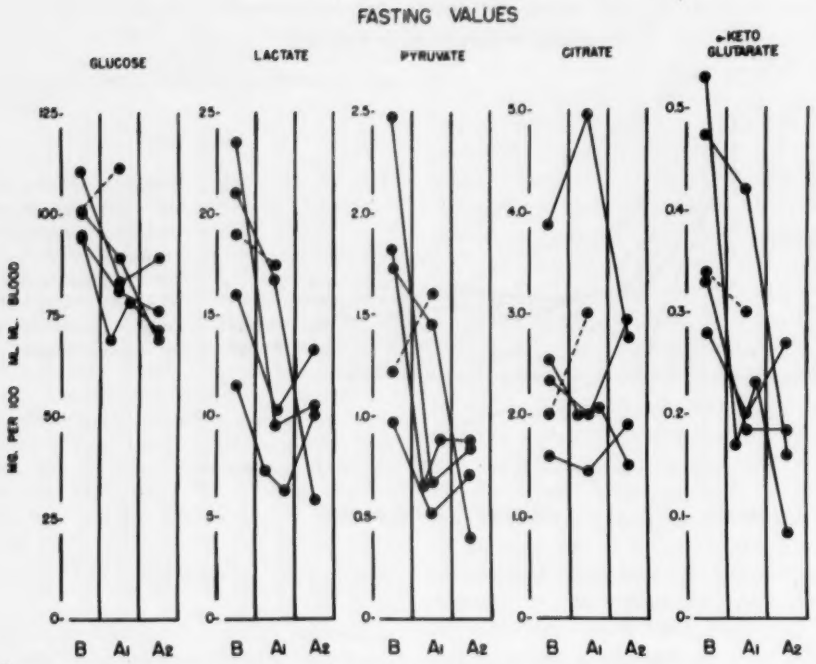

Fig. 2.—Fasting blood levels of the carbohydrate substances measured. *B* indicates values on a thiamin-free regimen; A_1 indicates values after addition of thiamin; A_2 indicates values on a full diet.

Fasting blood lactic acid levels were slightly or markedly elevated in all patients on the thiamine-free regimen. The addition of thiamine caused a fall in fasting blood lactic acid concentration in all, the fall resulting in normal values in three patients; the two exceptions included the patient who died. Subsequent administration of a full diet caused no change in the first three and a fall to normal in the surviving one of the other two (Fig. 2).

Fasting blood pyruvic acid levels were elevated in four of the five patients on the thiamine-free regimen. The addition of thiamine caused a fall to normal in three, the level showing no further change on the full diet. In one of the other two patients thiamine caused a partial fall toward normal, a greater fall later occurring on a full diet. The patient who died showed a slight rise after five days of thiamine therapy (Fig. 2).

The fasting plasma citric acid level was normal or elevated in all five patients on the thiamine-free regimen. Subsequent changes were variable (Fig. 2).

The fasting blood α-ketoglutaric acid level was markedly elevated in all five patients before the administration of thiamine. Giving thiamine caused a fall in the fasting level in all patients and a further fall in two of the four who subsequently received a full diet (Fig. 2).

The fasting pyruvate-lactate ratio was normal in three patients on the thiamine-free diet and was elevated in two—in one of these only slightly. Thiamine caused a fall in these ratios in only three cases. In a fourth case it remained unchanged but fell later when a full diet was given. One of the three patients who showed a fall in ratio on thiamine showed a further fall on a full diet. The fifth patient (the one who died) showed a rise in ratio even though

TABLE 2.—*Fasting Blood Pyruvate-Lactate Ratio ×100*

Case	Deficient Diet	Deficient Diet Plus Thiamine	Full Diet
Bu	10.6	7.1	7.4
Ba	8.3	5.1	5.3
Bo	15.7	11.6* (9.0, 14.2)	7.2
O	8.2	8.7	6.7
C	6.4	9.1	

*Average value.

his ocular manifestations of Wernicke's disease were much improved (Table 2).

B. Blood Concentrations After Administration of Dextrose.—The pyruvate-lactate ratio varied markedly after the administration of dextrose. The ratios fell significantly in only one of three patients after the administration of thiamine; it showed further decreases when this patient was on a full diet; it also decreased in another patient on a full diet (Table 3 and Fig. 4).

The changes in intermediary metabolism are best considered separately in the individual cases.

Case Ba (Fig. 5): Administration of dextrose gave rise to abnormal curves for blood glucose and for pyruvic and α-ketoglutaric acids while the patient was on the thiamine-free diet; the curves for blood lactic and citric acids were normal. Administration of thiamine improved the blood glucose and pyruvic acid curves; however, the blood α-ketoglutaric acid curve became more abnormal. On a full diet the patient showed normal curves in all categories, the curves for glucose and citric and α-ketoglutaric acids improving.

Case Bo (Fig. 6): While on a thiamine-free regimen this patient showed abnormal rises only in blood lactic and pyruvic acid levels after receiving dextrose. Giving thiamine caused no change of any kind in the two tests done after 7 and 21 days of thiamine administration. Administration of a full diet caused a return to normal of the curves for lactic and pyruvic acids and improvement of the citric acid curve (which initially was in the normal range).

Case C (Fig. 7): Administration of dextrose gave rise to abnormally elevated curves for blood glucose and lactic and pyruvic acids while the patient was on a thiamine-free regimen. Giving thiamine for five days

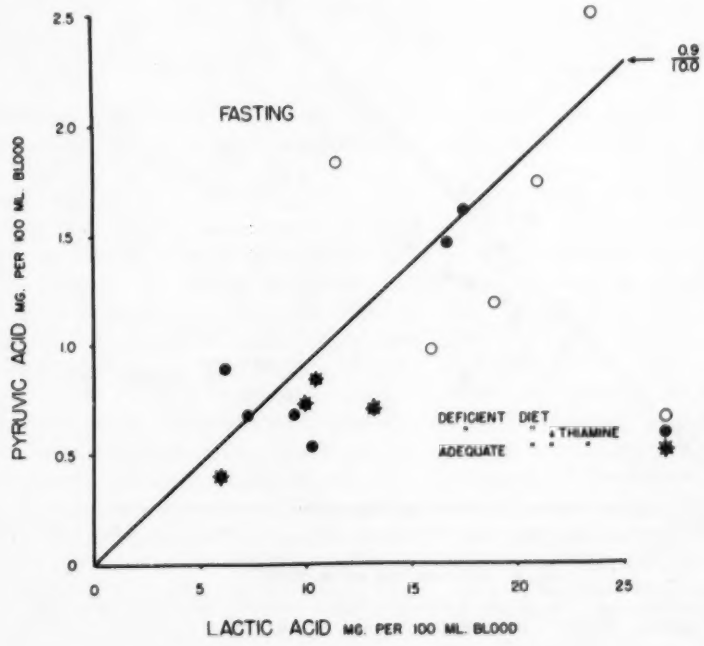

Fig. 3.—Relations between fasting pyruvate and lactate levels. The open circles show values before treatment; the solid dots show values after the administration of thiamine, and the stars show values after the administration of a full diet. The untreated patients showed a pyruvate-lactate ratio of 0.9:10.0.

TABLE 3.—*Blood Pyruvate-Lactate Ratio ×100 After Dextrose*

Case	Deficient Regimen	Deficient Diet Plus Thiamine	Full Diet
Ba	10.8* (10.7, 9.1, 10.5, 13.0)	8.8 (8.2, 9.2, 8.8)	7.6 (7.3, 8.1, 7.7, 7.2)
Bo	13.6 (15.1, 12.1)	12.3 (18.4, 12.8, 10.6, 10.0, 10.4, 12.5, 11.6)	6.9 (9.6, 4.5, 6.7)
C	8.9 (9.9, 10.2, 7.1, 8.5)	8.1 (8.0, 7.3, 7.4, 9.7)	

*Average value.

caused regression of the ocular manifestations of Wernicke's syndrome and restoration of lactate and pyruvate metabolism to normal; however, the dextrose tolerance worsened. The patient died unexpectedly about 48 hours after the test.

Comment

Evaluation of the findings of the present study is made difficult by the fact that most of the patients had hepatic disease and that some showed anemia.

The fact that all the patients but one (i. e., a total of 16 out of 17) had elevated fasting blood pyruvate levels before treatment seemingly establishes the value of this measurement as an index of thiamine deficiency. On the other hand, it has been reported that patients with cirrhosis of the liver may show a similar abnormality.[20-22] Judging from these reports, it required an advanced stage of the disease, such as hepatic coma, to disturb the pyruvic acid metabolism. In our patients the liver disease was comparatively mild, although the severity could not be judged precisely. How much this degree of liver disease contributed to the abnormality of pyruvate metabolism would be similarly difficult to determine. Moreover, the work of Earl and co-workers[16] showed that there is an abnormality of pyruvate metabolism in patients with untreated pernicious anemia and subacute combined degeneration of the spinal cord. Although the blood pyruvate levels were

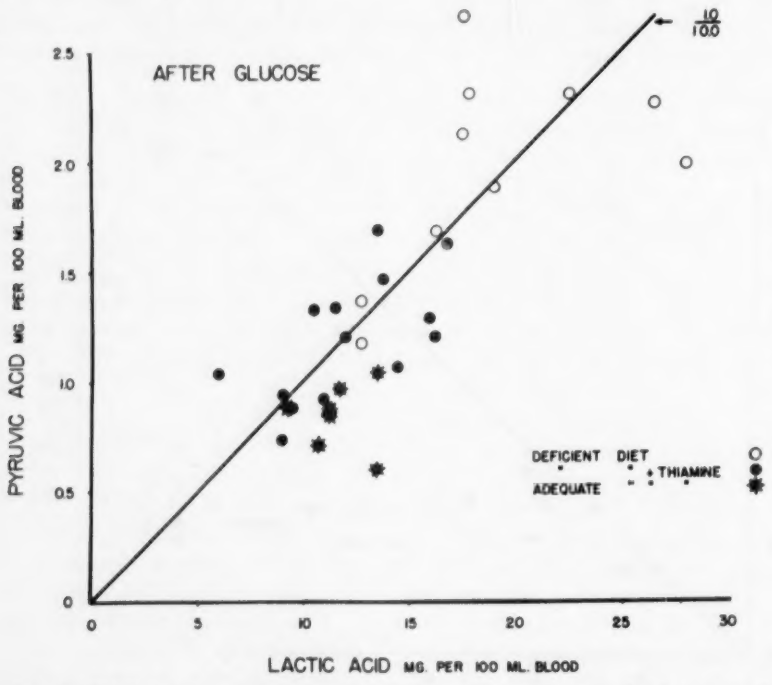

Fig. 4.—Relations between pyruvate and lactate levels after dextrose. Symbols as in Figure 2. The untreated patients showed a pyruvate-lactate ratio of 1.0:10.0.

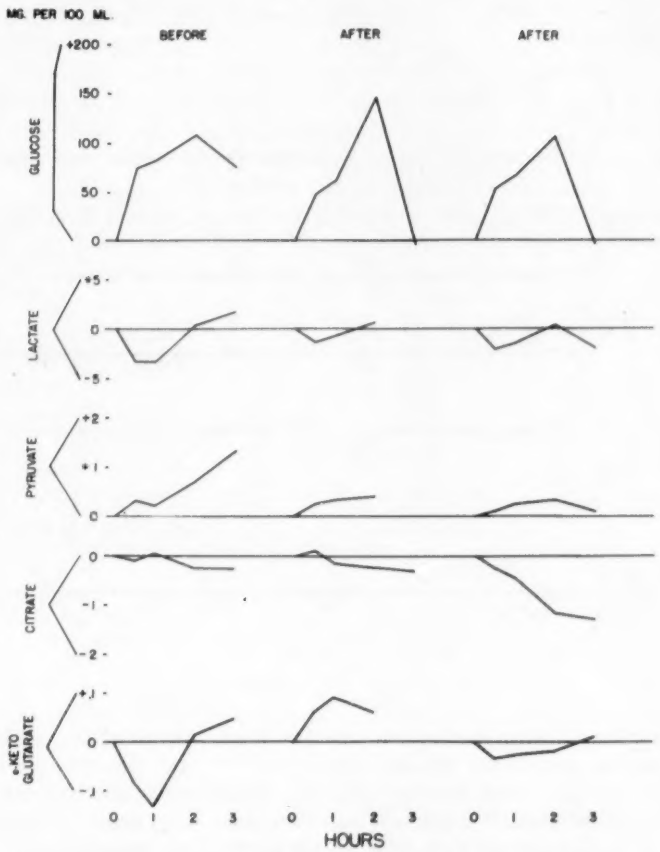

Fig. 5 (Case Ba).—Rises in blood constituents after 50 gm. of dextrose intravenously. "Before" indicates values on the thiamin-free regimen; the first "after" indicates findings following the addition of thiamine; the second "after" indicates findings on a full diet. Before treatment, the curves for glucose and for pyruvic and α-ketoglutanic acids were abnormal.

normal in the fasting state, they rose to abnormally high levels after administration of dextrose, these levels falling to normal after administration of vitamin B_{12}. It is evident that although an elevation in blood pyruvate concentration is characteristic, one cannot regard this change as specific evidence of thiamine deficiency. In addition, it should be noted that in the five patients studied in greatest detail, elevation of fasting levels of all blood carbohydrate constituents was found before treatment. The rise in blood pyruvate concentration was usually not elevated out of proportion to the other blood constituents studied. This finding casts serious doubt on the validity of the fasting pyruvate-lactate ratio as an index of thiamine deficiency in the cases here reported.

Results obtained after the administration of dextrose are likewise difficult to interpret. Of 13 patients so studied, 10 showed an abnormal rise of blood pyruvate concentration after receiving dextrose. In only one of the three patients studied in greatest detail was the rise of blood pyruvate level out of proportion to that of other blood carbohydrate constituents. One is not justified therefore in singling out the abnormal blood concentration of pyruvate after the administration of dextrose as the typical change in thiamine deficiency, at least as exemplified by patients with Wernicke's disease. It also follows that the use of the blood pyruvate-lactate ratio after dextrose as an index of thiamine deficiency is not valid. Excessive rises in blood pyruvate after dextrose administration occur not only

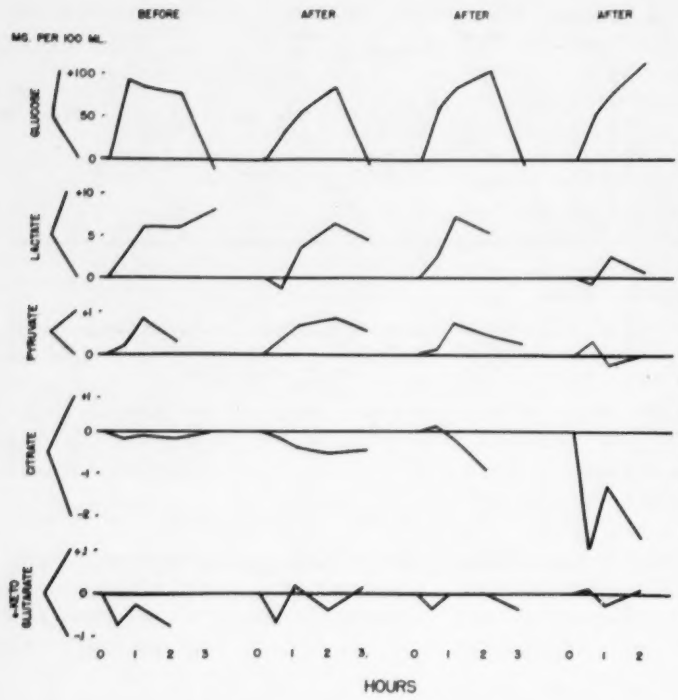

Fig. 6 (Case Bo).—Rises in blood constituents after 50 gm. of dextrose intravenously. "Before" indicates values on the thiamin-free regimen; the first and second "after" indicate the findings after the administration of thiamine; the third "after" indicates findings on a full diet. Before treatment, the curves for lactic and pyruvic acids were abnormal.

in severe liver disease but also in brain disease not due to thiamine deficiency.[14,15] It has also been reported that the blood pyruvate level after dextrose ingestion rises to an abnormally high level in adequately nourished alcoholic addicts[23,24]; a similar abnormality has also been reported in barbiturate addicts.[24]

The administration of thiamine was followed by the prompt onset of improvement in some of the ocular and mental signs of the Wernicke's syndrome. Some improvement in ocular movement could be detected as early as a few hours following the parenteral administration of thiamine, although several days to a week were required for the complete restitution of the ophthalmoplegia. In the mental sphere, the improvement was similarly dramatic; within hours after the administration of thiamine the patients became more alert, talkative, attentive, and cheerful. The ataxia and nystagmus also improved with thiamine alone, but more gradually; in almost every case they persisted in a mild form long after a full diet was instituted. With improvement in some of the mental signs, others (the memory defect) became more prominent. All our patients were left with a serious degree of memory impairment, i. e., Korsakoff's psychosis.

The ophthalmoplegia and some of mental signs reversed promptly with thiamine alone, and the same was generally but not always true of the abnormality in the fasting blood pyruvate levels. In this respect there was a rough correlation between the clinical and biochemical abnormalities and their response to thiamine. It was our impression that the latter lagged somewhat behind the former, although the relative infrequency of the biochemical estimations made it difficult to equate the clinical and biochemical abnormalities with absolute accuracy.

These observations are in general agreement with those of Wortis and co-workers,[13] as are our observations on the changes in

blood pyruvate following the administration of dextrose. Before treatment with thiamine, our patients showed an abnormal rise of blood pyruvate following dextrose, although this change was not found quite as consistently as the elevation of pyruvate in the fasting state.

The rise in blood pyruvate concentration after dextrose, as well as the changes in the pyruvate-lactate ratio were not regularly correlated with changes in the clinical status with respect to treatment with thiamine alone. In some respects the biochemical abnormalities did not reach their most nearly normal level for some weeks after the patient had been given a full diet in addition to therapeutic doses of thiamine; despite the biochemical improvement, there

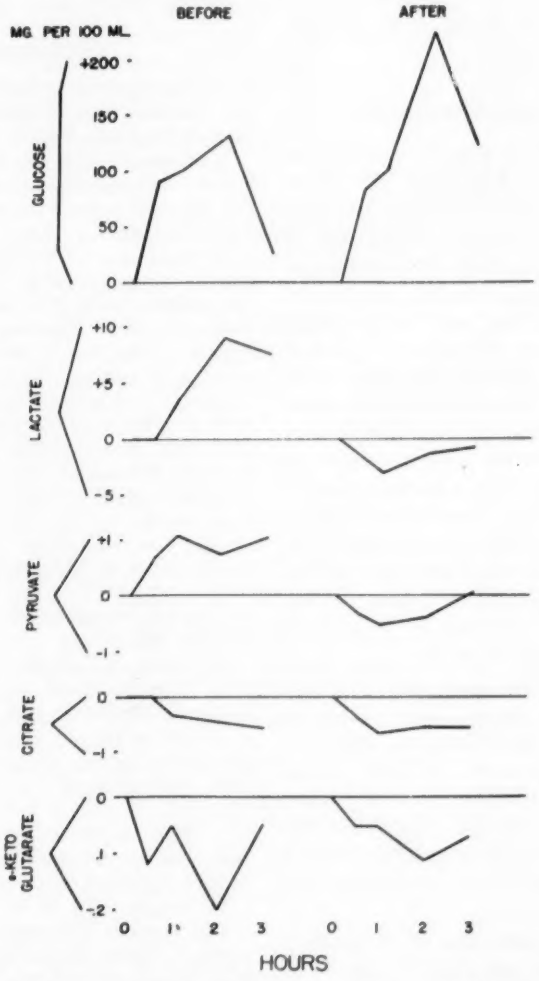

Fig. 7 (Case C).—Rises in blood constituents after 50 gm. of dextrose intravenously. "Before" indicates findings on the thiamin-free regimen; "after" indicates findings after thiamin. Before treatment the curves for glucose and lactic and pyruvic acids were abnormal.

was slight or no recognizable clinical change during the period of full diet. Moreover, even after the observed biochemical abnormalities had returned to normal the patients were left with considerable neurologic deficit, comprising nystagmus, ataxia, and Korsakoff's psychosis. However, the coexistence of apparent biochemical recovery and persistence of clinical evidence of disease should not be emphasized unduly, since the intravenous 50 gm. dextrose tolerance test used in the present study is not as sensitive an indicator of disturbed carbohydrate metabolism as the oral 100 gm. glucose tolerance test.

Summary and Conclusions

Seventeen patients with Wernicke's encephalopathy associated with alcoholism were studied; all but a few also had mild liver disease. A marked disturbance of carbohydrate intermediary metabolism was found: fasting blood levels of glucose and lactic, pyruvic, citric, and α-ketoglutaric acids were elevated, and abnormal rises in these constituents occurred after the intravenous infusion of dextrose. Of these various constituents, pyruvic and α-ketoglutaric acids were the most regularly affected. Following the administration of thiamine the fasting blood concentrations of the various carbohydrates studied fell, but usually did not reach their lowest level for several weeks, and responses to dextrose also became normal in some cases only after a prolonged period.

An elevation of the fasting blood pyruvate concentration and, to a smaller extent, an abnormal rise in blood pyruvate after dextrose are characteristic, but not specific abnormalities in patients with Wernicke's syndrome. The fasting pyruvate-lactate ratio or pyruvate-lactate ratio after dextrose proved to be poor indices of thiamine deficiency.

With the administration of thiamine, a rough correlation pertained between the reversal of ophthalmoplegia and apathy and the fall in the fasting blood pyruvate levels, the latter lagging behind the former. In other respects the biochemical abnormalities correlated poorly with the clinical changes.

The patients who formed the subjects of this investigation were studied on the medical wards of the Boston City Hospital. Dr. William B. Castle, director of the second and fourth (Harvard) medical services, Dr. Fernando Biguria, director of the first and third (Tufts) medical services, and Dr. Kermit Katz, director of the fifth and sixth (Boston University) medical services, made it possible for us to study these patients. The many house officers of the medical services also cooperated in this work.

McLean Hospital (Dr. Altschule).

REFERENCES

1. Spillane, J. D.: Nutritional Disorders of the Nervous System, Baltimore, Williams & Wilkins Company, 1947, p. 82.

2. Campbell, A. C. P., and Russell, W. R.: Wernicke's Encephalopathy: The Clinical Features and Their Probable Relationship to Vitamin B Deficiency, Quart. J. Med. 10:41-51, 1941.

3. Alexander, L.: Wernicke's Disease: Identity of Lesions Produced Experimentally by B_1 Avitaminosis in Pigeons with Hemorrhagic Polioencephalitis Occurring in Chronic Alcoholism in Man, Am. J. Path. 16:61-70, 1940.

4. de Wardener, H. E., and Lennox, B.: Cerebral Beri-Beri (Wernicke's Encephalopathy): Review of 52 Cases in a Singapore Prisoner-of-War Hospital, Lancet 1, 11-17, 1947.

5. Cruickshank, E. K.: Wernicke's Encephalopathy, Quart. J. Med. 19:327-338, 1950.

6. Phillips, G. B.; Victor, M.; Adams, R. D., and Davidson, C. S.: A Study of the Nutritional Defect in Wernicke's Syndrome: Effect of Purified Diet, Thiamine, and Other Vitamins on Clinical Manifestations, J. Clin. Invest. 31: 859-871, 1952.

7. Jolliffe, N.; Wortis, H., and Fein, H. D.: The Wernicke Syndrome, Arch. Neurol. & Psychiat. 46:569-597, 1941.

8. Victor, M., and Adams, R. D.: The Effect of Alcohol on the Nervous System, Proc. A. Res. Nerv. & Ment. Dis., Proc. (1952) 32:526-573, 1953.

9. Platt, B. S., and Lu, G. D.: Chemical and Clinical Findings in Beri-Beri, Quart. J. Med. 5:355-373, 1936.

10. Thompson, R. H. S., and Johnson, R. E.: Blood Pyruvate in Vitamin B_1 Deficiency, Biochem. J. 29:694-700, 1935.

11. Peters, R. A.: The Biochemical Lesion in Vitamin B_1 Deficiency, Lancet 1:1161-1165, 1936.

12. Banga, I.; Ochoa, S., and Peters, R. A.: Pyruvate Oxidation in Brain, Biochem. J. 33: 1109-1121, 1939.

13. Wortis, H.; Bueding, E.; Stein, M. H., and Jolliffe, N.: Pyruvic Acid Studies in the Wernicke Syndrome, Arch. Neurol. & Psychiat. 47:215-222, 1942.

14. Jones, H. H.; Jones, H. H., Jr., and Bunch, L. D.: Biochemical Studies in Multiple Sclerosis, Ann. Int. Med. 33:831-840, 1950.

15. Henneman, D. H.; Altschule, M. D.; Goncz, R. M., and Alexander, L.: Carbohydrate Metabolism in Brain Disease: 1. Glucose Metabolism in Multiple Sclerosis, A. M. A. Arch. Neurol. & Psychiat. 72:688-695, 1954.

16. Earl, C. J.; El Hawary, M. F. S.; Thompson, R. H. S., and Webster, G. R.: Blood-Pyruvate Levels in Subacute Combined Degeneration of Cord: Effect of Vitamin B_{12} Therapy, Lancet 1:115-116, 1953.

17. Barker, S. B., and Summerson, W. H.: The Calorimetric Determination of Lactic Acid in Biological Material, J. Biol. Chem. 138:535-554, 1941.

18. Friedemann, T. E., and Haugen, G. E.: Pyruvic Acid: II. The Determination of Keto Acids in Blood and Urine, J. Biol. Chem. 147: 415-442, 1943.

19. Henneman, D. H.; Altschule, M. D., and Goncz, R. M.: Carbohydrate Metabolism in Brain Disease: II. Glucose Metabolism in Schizophrenic, Manic-Depressive, and Involutional Psychoses, A. M. A. Arch. Int. Med. 94: 402-416, 1954.

20. Snell, A. M., and Butt, H. R.: Hepatic Coma: Observations Bearing on its Nature and Treatment, Tr. A. Am. Physicians 56:321-329, 1941.

21. Amatuzio, D. S.; Shrifter, N.; Stutzman, F. L., and Nesbitt, S.: Blood Pyruvic and Response to Intravenous Glucose or Insulin in the Normal and in Patients with Liver Disease and with Diabetes Mellitus, J. Clin. Invest. 31:751-755, 1952.

22. Smith, L. H., Jr.; Ettinger, R. H., and Seligson, D.: A Comparison of the Metabolism of Fructose and Glucose in Hepatic Disease and Diabetes Mellitus, J. Clin. Invest. 32:273-282, 1953.

23. Varela, A.; Penna, A.; Alcaino, F.; Johnson, E., and Mardones, J.: Sugar, Pyruvate and Acetaldehyde Levels in the Blood of Alcohol Addicts After Ingestion of Dextrose, Quart. J. Stud. Alcohol 14:174-180, 1953.

24. Hunter, R. A.; Merivale, W. H. H., and Smith, A. J.: Disturbances of Carbohydrate Metabolism Caused by Barbiturates and Alcohol, Lancet 2:1353-1355, 1955.

Carbohydrate Metabolism in Brain Disease

IX. Carbohydrate Metabolism in the Chronic Alcoholic Psychoses

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Earlier work has shown that patients with schizophrenic, manic-depressive, and involutional psychoses have a disorder of carbohydrate metabolism [1] that is indistinguishable from one exhibited by nonpsychotic patients with a chronic brain disease, i. e., multiple sclerosis.[2] The present report describes certain aspects of carbohydrate metabolism in another brain disease—chronic alcoholic psychosis. Actually, the patients discussed here constituted two groups: (*a*) those with Korsakoff's psychosis and (*b*) those with chronic auditory hallucinosis associated with alcoholism.

Material and Methods

Nine patients were studied; all were women. One group consisted of four patients, aged 31, 49, 60, and 62 years, respectively, with the classic features of Korsakoff's psychosis—impairment of memory, confabulation, and an inability to learn and retain newly presented material. All four patients had a background of serious alcoholism and still showed the stigmata of a previous attack of Wernicke's encephalopathy in the form of horizontal nystagmus and slight ataxia. At the time of our testing they had been in the mental hospital for periods ranging from two to six years and appeared well nourished.

A second group consisted of five patients, aged 37, 41, 58, 70, and 71, years respectively, with chronic auditory hallucinosis. At the time of our testing they had been institutionalized for periods ranging from 3 to 19 years and were free of nutritional or other physical illnesses. Their illness originally took the form of an acute alcoholic hallucinosis—that is, it was characterized by the presence of vivid auditory hallucinations and behavior which was abnormal but appropriate to the hallucinatory content. In distinction to most instances of acute alcoholic hallucinosis, the symptoms did not subside quickly and completely. Instead, the hallucinations persisted, poorly systematized delusions became prominent, and the patient's behavior became inappropriate. At this stage the illness was difficult to distinguish from paranoid schizophrenia. In the background of our patients there were several features, however, which would be decidedly unusual in schizophrenia. The symptoms began at a later age (ranging from 32 to 60 years) than one usually encounters in schizophrenia; the prepsychotic personality of our patients was of the extroverted type, and not of the type that is generally considered characteristic of schizophrenia; finally, all the patients in this group had a background of severe and prolonged alcoholism, and the final illness developed in close temporal relationship to particularly heavy drinking.

Observations were made with the patient at rest in bed after a fast of 14 hours. After fasting blood samples were taken the patients were given 100 gm. of glucose by mouth; blood samples were taken at hourly intervals thereafter for three hours. The methods used were as described in previous articles in this series.[1,2] Normal values for true blood glucose and pyruvic, lactic, citric, and α-ketoglutaric acids, both in the fasting state and at intervals following the ingestion of 100 gm. glucose, have also been previously determined.[1,2] The mean values of these constituents in normal subjects and psychotic patients[2] are shown in Figure 1.

Observations

A. Chronic Korsakoff's Psychosis.—The fasting levels of blood glucose and of lactic, pyruvic, citric, and α-ketoglutaric acids were normal in all four patients studied (Table 1). Administration of glucose by mouth revealed abnormalities in carbohydrate metabolism in all four patients. One (Case T,

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From the Laboratory of Clinical Physiology, McLean Hospital, Waverley, Mass., the Department of Neurology, Massachusetts General Hospital, Boston, and the Departments of Medicine and Neurology, Harvard Medical School, Boston.

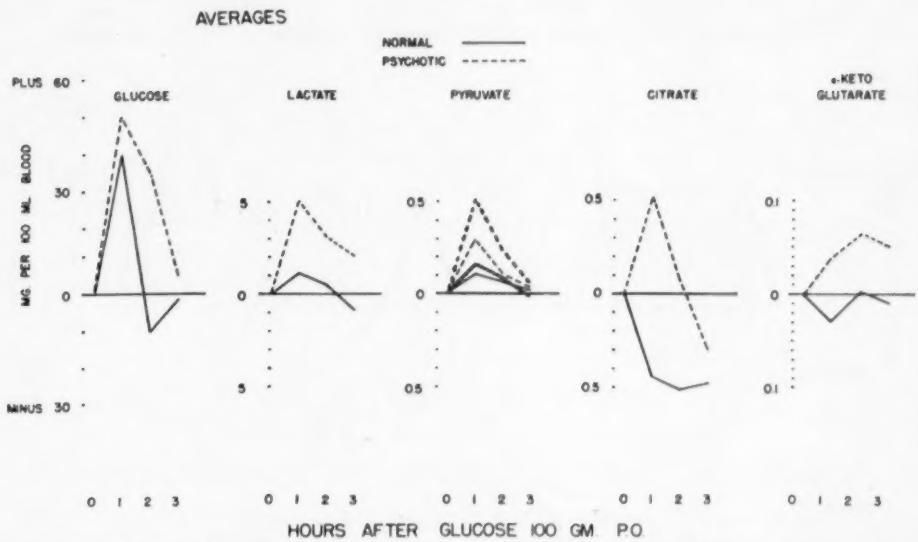

Fig. 1.—Average changes after glucose, 100 gm. by mouth, in normal subjects (solid lines) and in patients with schizophrenic, manic-depressive, and involutional psychoses. The two sets of lines for pyruvate changes indicate values obtained by two different methods.

TABLE 1.—*Fasting Values of Blood Constituents in Korsakoff's Psychosis Due to Alcoholism*

Case	Glucose, Mg./100 Ml.	Lactate, Mg./100 Ml.	Pyruvate, Mg./100 Ml.	Citrate, Mg./100 Ml.	α-Keto glutarate, Mg./100 Ml.
T	73	12.8	0.58	2.30	0.17
No	84	14.5	0.78	1.68	0.14
B	84	10.3	0.66	2.16	0.09
Ct	63	12.5	0.77	1.27	0.17
Averages	76	12.5	0.70	1.86	0.14

Fig. 2) showed abnormal rises in blood glucose, lactate, and pyruvate concentrations; two (Cases No and B, Figs. 3 and 4) showed abnormal rises in blood lactate and α-ketoglutarate concentrations and one (Case Ct, Fig. 5) showed abnormal rises in blood glucose and lactate concentration.

B. Postalcoholic Schizophrenic Syndrome.—The fasting values for blood glucose and for lactic, pyruvic, citric, and α-ketoglutaric acids were normal in all the five patients studied (Table 2). Administration of glucose revealed abnormalities in carbohydrate metabolism in all three of the patients in whom the test was done. One (Case Ca, Fig. 6) showed abnormal rises in blood glucose, lactate, pyruvate, and α-ketoglutarate concentrations; one (Case F, Fig. 7) showed abnormal rises in blood glucose, lactate, and pyruvate concentrations, and one (Case Co, Fig. 8) showed only an abnormal rise in blood citrate level.

Comment

The findings of the present study show that patients with chronic alcoholic psychoses exhibit disturbances in carbohydrate metabolism. The same abnormalities are found both in Korsakoff's psychosis and in chronic auditory hallucinosis, despite the fact that these states are dissimilar clinically, and probably pathologically and etiologically.[8] Furthermore, the chemical changes in the alcoholic psychoses are indistinguishable from those seen in schizophrenic, manic-depressive, and involutional psychoses [1]; the changes are also identical with

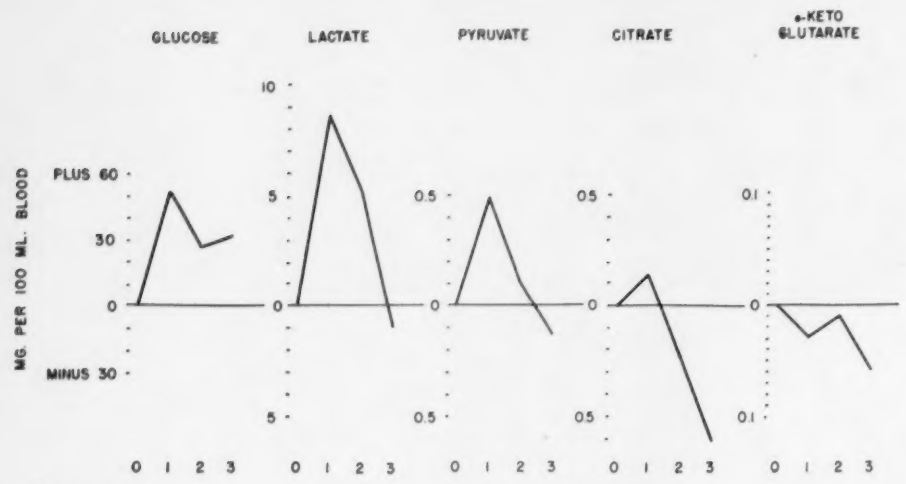

Fig. 2.—Effect of glucose, 100 gm. by mouth, in Case T.

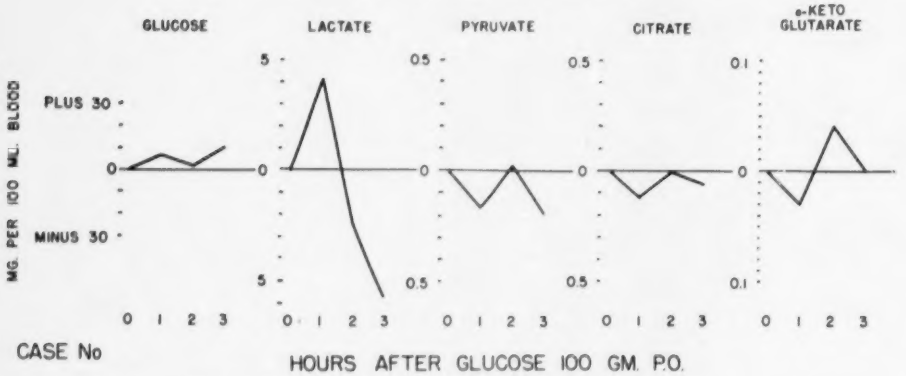

Fig. 3.—Effect of glucose, 100 gm. by mouth, in Case No.

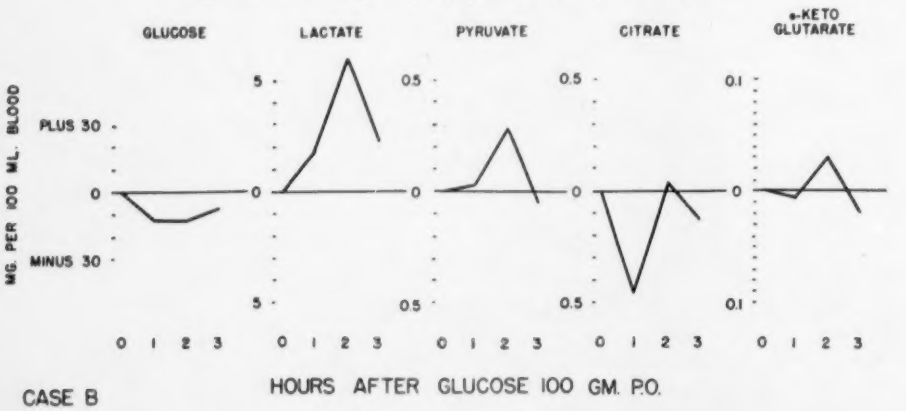

Fig. 4.—Effect of glucose, 100 gm. by mouth, in Case B.

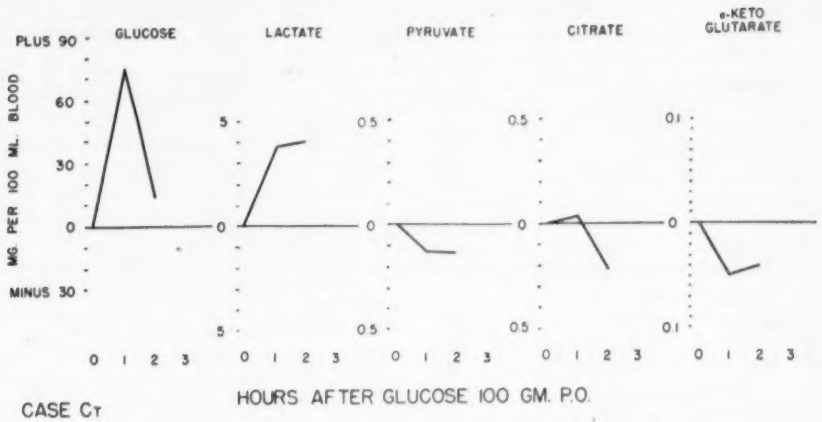

Fig. 5.—Effect of glucose, 100 gm. by mouth, in Case Ct.

TABLE 2.—*Fasting Values of Blood Constituents in Chronic Alcoholic Auditory Hallucinosis*

Case	Glucose, Mg./100 Ml.	Lactate, Mg./100 Ml.	Pyruvate, Mg./100 Ml.	Citrate, Mg./100 Ml.	α-Keto glutarate, Mg./100 Ml.
Ca	81	9.0	0.84	1.98	0.12
F	66	10.0	0.93	2.58	0.20
Co	77	12.8	0.85	2.20	0.10
R	88	7.5	0.79	2.48	0.12
Ba	78	8.5	0.92	2.97	0.11
Averages	78	9.6	0.87	2.44	0.13

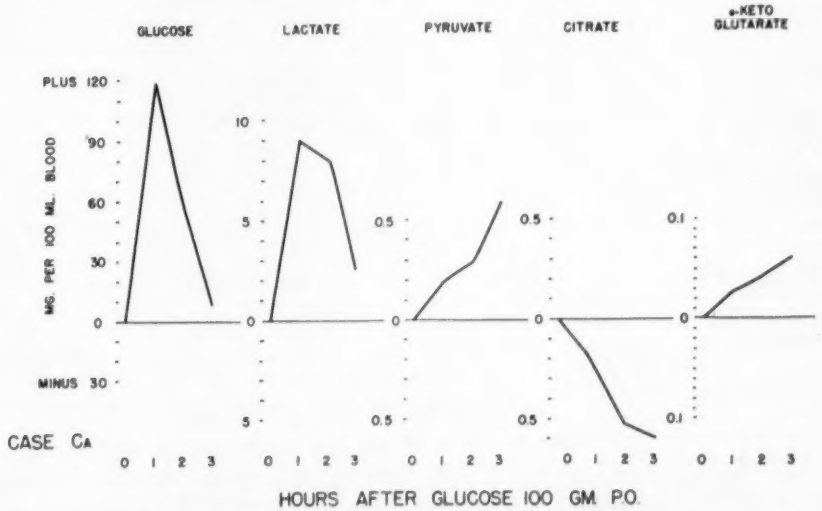

Fig. 6.—Effect of glucose, 100 gm. by mouth, in Case Ca.

those observed in nonpsychotic patients with multiple sclerosis.[2]

The observations made on the patients with alcoholic psychoses provides another example of a disease of the nervous system characterized by a disorder of carbohydrate intermediary metabolism. The mechanism of this disorder is not known; in fact, it is difficult to define the common denominator in this group of diseases in terms other

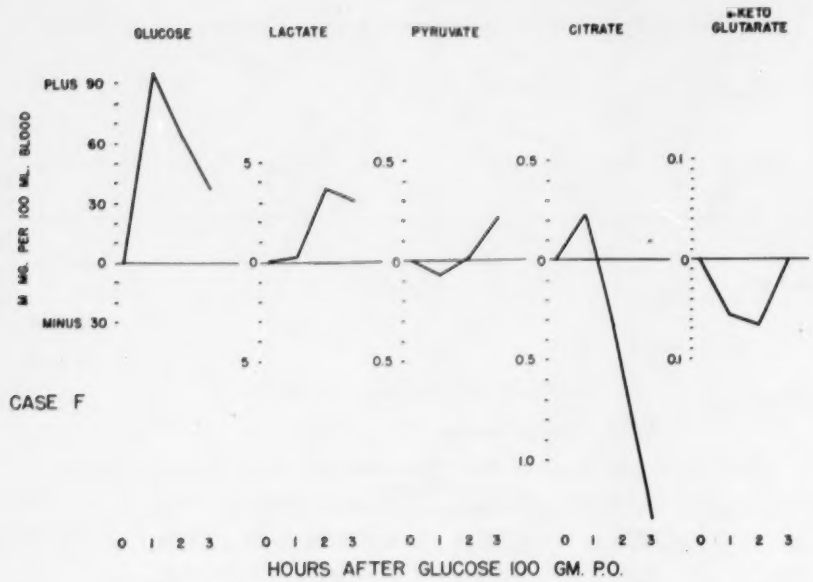

Fig. 7.—Effect of glucose, 100 gm. by mouth, in Case F.

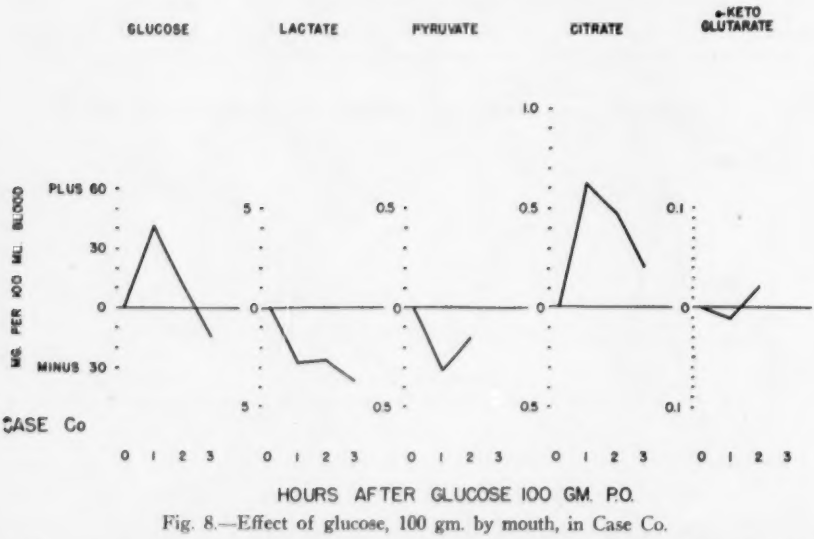

Fig. 8.—Effect of glucose, 100 gm. by mouth, in Case Co.

than their common cerebral location. At least some of the features of this metabolic disorder also occur in a wide variety of noncerebral disorders.[4]

Summary and Conclusions

Patients with chronic Korsakoff's psychosis, and patients with a paranoidhallucinatory syndrome due to chronic alcoholism, show abnormalities in carbohydrate metabolism after the ingestion of glucose. These abnormalities are indistinguishable from those seen (*a*) in patients with schizophrenic, manic-depressive, and involutional psychoses and (*b*) in nonpsychotic patients with multiple sclerosis.

Appendix

CASE 1.—A 62-year-old woman was admitted to the Boston State Hospital on Jan. 12, 1950. One month previously she had been admitted to the Boston City Hospital because of the acute onset of confusion and a bilateral abducens palsy. She had been drinking heavily for 20 years and had eaten an inadequate diet for several years. The ophthalmoplegia cleared rapidly, but she remained disoriented and showed a marked degree of confabulation and memory defect, particularly for recent events. She was regarded as a typical instance of Korsakoff's psychosis. At the Boston State Hospital these features persisted. In 1955 she was still disoriented in time and place. Although she gave a good account of her early life, she could recall virtually nothing of the circumstances surrounding her admission or of any events since that time. Simple facts, such as the time, date, or examiner's name, had to be repeated several times, and then were retained by the patient for only a few minutes. Insight and judgment were lacking. There was a fine horizontal nystagmus on lateral gaze to both sides, but otherwise there were no abnormalities in the neurological or general physical examination.

Diagnosis.—Korsakoff's psychosis.

CASE 2.—A 60-year-old woman was admitted to the Boston State Hospital on Feb. 12, 1954. At that time she was described as quiet and cooperative, but mildly euphoric, disoriented, and confabulating. She also had an enlarged liver, a mild anemia, and the signs of polyneuropathy. A past history of severe alcoholism and poor dietary habits was elicited from relatives. On examination two years later, she realized that she was in a hospital but could not name the institution. She was disoriented in time and thought she had been here for only three weeks. Events which occurred before 1930 or thereabout were adequately described, but her memory was badly defective for later events. She was unable to remember the simplest facts for more than five minutes. She appeared well nourished, and there was no longer any anemia or evidence of liver disease. Ankle jerks were still absent, her gait was mildly ataxic, and she showed a horizontal nystagmus on lateral gaze.

Diagnosis.—Korsakoff's psychosis.

CASE 3.—A 31-year-old woman was admitted to the Boston State Hospital on April 10, 1953. She had been a heavy drinker for many years. In October, 1952, after several weeks of absenteeism from work, she was discovered in her room, confused and bedridden. The patient was at first attended by her mother, but was finally admitted to the Boston City Hospital in February, 1953. At that time the following abnormalities were noted: a coarse horizontal nystagmus on lateral gaze; marked thinness of the limbs, inability to walk without support, absent deep tendon reflexes, distal symmetrical sensory loss affecting the legs; an abnormal mental state characteristic of Korsakoff's psychosis. Following her transfer to the state hospital, there was an improvement in general nutrition and a reversal of the polyneuropathy, but the patient was left with absent knee and ankle jerks and a serious impairment of memory.

Diagnosis.—Korsakoff's psychosis.

CASE 4.—A 49-year-old woman was committed to the Boston State Hospital on Aug. 15, 1953, from a local jail, following an arrest for drunkenness. Her alcoholic excess was of at least 10 years' duration, and she had been hospitalized on two occasions for delirium tremens. On examination the only neurologic abnormality was a horizontal nystagmus on lateral gaze. In the mental sphere, the major defect was in memory and in her ability to learn and to recall newly presented material. Given three simple facts, she could recall only one after a period of two minutes.

Diagnosis.—Korsakoff's psychosis.

CASE 5.—A 37-year-old woman was admitted to the Boston State Hospital on Feb. 26, 1953, because of hallucinations of five days' duration. The patient had always been an extroverted, boisterous person and an excessive drinker for at least five years. Five days before admission she became restless and nervous. She saw people across the street shining flashlights in her eyes; she heard two men plotting to kill her and thought that a dope ring was using a radar machine to drive her insane. These hallucinations and delusions were extremely vivid, and the patient was appropriately fearful. The physical and neurological examinations were normal. Her memory was unimpaired, as was her capacity for abstract thinking. There was no incoherence or irrelevance of thought. She was overactive, apprehensive, and deluded, and she heard voices calling her foul names and threatening to kill her. Over the ensuing months she passed into a quiescent state, in which she was still deluded and hallucinated but showed no agitation. Her associations were tangential and her thought processes at times incomprehensible; she was casual toward the voices, and her affective response was bland and inappropriate. Her state was regarded as characteristic of paranoid schizophrenia.

Diagnosis.—? Chronic alcoholic auditory hallucinosis; ? paranoid schizophrenia.

CASE 6.—A 41-year-old woman was admitted to the Boston State Hospital in December, 1945. For nine years before this she had been drinking whiskey, ale, and wine daily; she was frequently found drunk by her husband on his return from work. The patient was always outgoing in nature

and made friends easily. She was perfectly well until 17 weeks before this admission, when she suddenly began to hear voices; they belonged to a man and woman whom she knew; the voices came from across the street and reproached her for drinking. The patient seemed intact in other respects, and a diagnosis was originally made of "alcoholic psychosis, chronic hallucinosis." The patient has continued to hallucinate until the present time, and her demeanor on repeated examination was characteristically schizophrenic. Her affective response was flat and at times inappropriate, remaining the same regardless of the thought content. There was a marked disturbance of logic and associations; her speech showed echolalia and the frequent use of neologisms and was constantly interrupted by grimacing and mannerisms.

Diagnosis.—? Chronic alcoholic auditory hallucinosis; ? paranoid schizophrenia.

CASE 7.—A 58-year-old woman was well until 1947, when she began to drink excessively. She was arrested many times for drunkenness; following such an episode in January, 1953, she was committed to the Boston State Hospital. On examination there were no abnormalities in the general physical or neurological examination. She had auditory and olfactory hallucinations. Her thought processes were markedly illogical, and the associations were bizarre and difficult to follow. Her affective response was totally inadequate; she related a long series of persecutions without a show of appropriate emotional response. Insight was lacking; memory was intact.

Impression.—Schizophrenic-like reaction in a chronic alcoholic; onset at age 56, without the premorbid personality generally associated with schizophrenia.

CASE 8.—A 71-year-old woman was first admitted to the Boston State Hospital on April 23, 1937. Since age 20 she had been given to long periodic bouts of drinking. About two weeks before admission she had the abrupt onset of visual and auditory hallucinations, to which she reacted in an appropriately fearful and agitated manner. She recovered from this episode in three weeks and was discharged without evidence of psychosis. In the next two years there were four separate admissions for similarly circumscribed episodes of alcoholic hallucinosis. Her final admission was in May, 1949; this time, however, her hallucinations and delusions persisted. Judging from the hospital record, her mental state has changed little over the years. She is fully oriented, and her memory is intact. She is constantly hearing voices and harbors poorly defined paranoid delusions, but remains cheerful and unperturbed despite their threatening content.

Diagnosis.—Chronic hallucinatory-delusional state, ? alcoholic, ? schizophrenic.

CASE 9.—A 70-year-old woman had been without any serious illness until 1940, when she was admitted to the Boston State Hospital in a hallucinated, agitated, and evertalkative state. This was thought to be an acute alcoholic psychosis, in view of her alcoholic history. She soon became calm and composed, but remained hallucinated and deluded, in which state she has remained to the present time. When last examined, in January, 1956, she was still hearing voices coming through the walls, cursing and calling her foul names. She reacted appropriately for the most part and carried on an animated conversation with these voices, to the extent where it was difficult to gain her attention. She firmly believed in their reality. Otherwise her thinking seemed normal; orientation and memory were intact.

Impression.—Chronic auditory hallucinosis, alcoholic.

Dr. Walter Barton, Superintendent, The Boston State Hospital, and the members of his staff gave permission for us to carry out this study.

McLean Hospital.

REFERENCES

1. Henneman, D. H.; Altschule, M.D., and Goncz, R. M.: Carbohydrate Metabolism in Brain Disease: II. Glucose Metabolism in Schizophrenic, Manic-Depressive, and Involutional Psychoses, A. M. A. Arch. Int. Med. 94:402-416, 1954.

2. Henneman, D. H.; Altschule, M. D.; Goncz, R. M., and Alexander, L.: Carbohydrate Metabolism in Brain Disease: I. Glucose Metabolism in Multiple Sclerosis, A. M. A. Arch. Neurol. & Psychiat. 72:688-695, 1954.

3. Victor, M., and Adams, R. D.: The Effect of Alcohol on the Nervous System, Proc. A. Res. Nerv. & Ment. Dis., Proc. (1952) 32:526-573, 1953.

4. Altschule, M. D.: Bodily Physiology in Mental and Emotional Disorders, New York, Grune & Stratton, Inc., 1953.

The Nature of Essential Hypertension

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The concept of essential hypertension needs clarification. Too much confusion and too many controversial statements are found in the immense literature on the subject. This is not due to insufficient knowledge of facts and analytical data from both clinic and laboratory, but rather to lack of satisfactory synthesis which would logically integrate all the facts—not only the personally convenient ones—into a system. What are some of the more important discrepancies concerning the nature of essential hypertension?

Discrepancies

1. There are authorities who consider the very term essential hypertension as a confession of ignorance[1,2] or as a collective concept for a number of conditions having in common the positive characteristic of arterial hypertension and the negative one of the absence of primary renal disease,[1] in other words, as designation of a syndrome rather than of a disease. British investigators recently "suspect that essential hypertension has no real existence as a specific clinical entity. It is a convenient term for those subjects whose arterial pressures exceed a certain level chosen on arbitrary grounds and in whom there is no other disease present that accounts for the high pressure."[3]

2. Some persons with excessive essential hypertension can live without particular symptoms for decades, others may succumb to a rapidly progressive variety of essential hypertension within a few years or months.

3. Many believe that the etiology of essential hypertension is unknown, although they admit that a hereditary factor "plays a role." They disregard the fact that heredity is etiology of its own.

4. A few authors stick stubbornly to the concept of primary renal pathogenesis of essential hypertension, ignoring the overwhelming arguments that militate against it (see also the definition of essential hypertension mentioned above).

5. Psychodynamically oriented clinicians believe that essential hypertension is caused by emotional factors, in particular personalities with aggressive and hostile tendencies which developed in childhood. For the unbiased reader this opinion is not acceptable because the same personality types may be found in persons with different other diseases or without any disease at all.

If we want to understand essential hypertension we must take into consideration two fundamental facts: (*a*) Different pathologic processes of various organs may cause arterial hypertension as one of their clinical manifestations. As a matter of fact, these types of hypertension are known as secondary or symptomatic hypertension and are different from essential or primary hypertension. (*b*) A normal healthy person maintains his blood pressure remarkably constant in spite of its frequent temporary alterations resulting from environmental and intrinsic influences. In other words, homeostasis of blood pressure throughout life is an essential characteristic of normal human beings.

(*a*) *Symptomatic Hypertension.*—This is encountered in diseases of the uropoietic system, such as glomerulonephritis, advanced pyelonephritis, polycystic kidney, and increased urinary back-pressure with subsequent hydronephrosis. A humoral factor, renin, produced by an ischemic kidney, has been recognized as pathogenetic agent. Symptomatic hypertension accompanies definite endocrine diseases, such as pheo-

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chromocytomas, adrenal cortical tumors, or pituitary hyperfunction with release of excessive amounts of corticotropic hormone (Cushing's disease). Lesions of hypothalamic centers or of the peripheral moderators in the ninth and tenth cranial nerves may cause symptomatic hypertension. Abnormalities and diseases of peripheral blood vessels may raise the blood pressure, such as coarctation of the aorta, polyarteritis nodosa, or arteriolosclerosis. The pathogenetic mechanism of each of these types of symptomatic hypertension is different. Hormones, abnormal function of vasomotor centers and nervous regulators, and mechanically increased peripheral vascular resistance are involved.

(*b*) *Homeostasis of Blood Pressure.*—This does not mean that the individual habitual blood pressure remains invariable, it means rather that it is brought back again to the original level if it had been altered temporarily by various factors both physical and psychic. It has become customary to designate the conditions brought about by such factors as "stress." Stress has been aptly defined as a collective term used at present to describe a change in circumstance or environment. Stress may lower the blood pressure to the point of fainting (syncope); much more often it raises the blood pressure, whether it is muscular exercise, anxiety, some other emotional upset or an extrinsic physical influence.

Every person is continuously exposed to vasopressive stress factors. If the homeostatic "feed-back mechanism" becomes deficient and the normal reduction of a physiologic temporary elevation of blood pressure fails to occur, the stage for the development of permanent hypertension is set.

How Is the Homeostasis of Blood Pressure Brought About?

Nervous and hormonal factors are intimately interlocked. The general principle of homeostasis depends upon the fundamental attribute of living organisms, that is, the ability of adaptation. Any disturbance of the *"milieu intérieur"* (Claude Bernard) is reacted upon by adaptive functional alterations. Remember the complex interaction of endocrine glands and nervous system in maintaining a normal blood sugar level or the regulatory function of the pituitary in securing a normal level of thyroid, adrenal cortical, and sex hormones. Higher cerebral functions are involved as well in certain adaptive processes. Adrenalectomized rats consume excessive amounts of sodium chloride, parathyroidectomized rats choose calcium, and experimentally exhausted rats prefer dextrose to calorically useless but similarly tasting saccharine solutions in a self-selected diet ("cafeteria-style" feeding experiments). Thus behavior is included in the adaptive mechanism.[4]

There is reason to assume that homeostasis of blood pressure is brought about by complex interaction of many factors concerned with the regulation of blood pressure. Even the proper adjustment of blood pressure to posture and to variable demands for blood supply in different regions of the body according to the normal activity of the person requires a delicate device. This device implies (1) a normal elasticity and normal reactivity of the arteriolar (and, more generally, vascular) walls to nervous and humoral stimuli; (2) a normal function of the vasomotor nervous system with all its branches, including the blood pressure restrainers of the carotid sinus and depressor nerves and diencephalic and higher cerebral centers that mediate the repercussions of emotions upon blood circulation; (3) the proper and adequate liberation of hypertensive and hypotensive substances which, in turn, depends on a normal function of certain endocrine glands, chiefly the adrenals, and their prompt and adequate response to nervous and humoral stimuli.

Hypertensive substances are epinephrine, arterenol, cortical steroids delivered by the adrenals, arterenol also produced in the wall of peripheral arteries by adrenergic nerve endings, corticotropic hormone, and

vasopressin liberated from the pituitary, vasoexcitor material (VEM of Shorr) released from the kidney as response to fall of blood pressure and to decreased renal blood flow, renin produced by an ischemic kidney, serotonin from various tissues, and perhaps encephalin from the brain, which, however, may be identical with arterenol.

Hypotensive substances probably involved in the regulation of blood pressure are the ubiquitous histamine, acetylcholine, the vasodepressor material (VDM) produced by the liver and identified as ferritin (E. Shorr), and amine oxidase around sympathetic nerve endings chiefly in blood vessels. This enzyme destroys arterenol and to a lesser extent epinephrine; it is for the sympathetic transmitter arterenol what cholinesterase is for the parasympathetic transmitter acetylcholine.

Many of these nervous and humoral factors that are capable of raising or lowering the blood pressure are links in the chain which secures homeostasis.

The Problem of Essential Hypertension

Now we are ready to tackle the problem of essential hypertension, keeping in mind two well-established facts: Essential hypertension is primarily a functional state without anatomical basis; heredity causes predisposition to its development.

The blood pressure measured in the office or clinic is somewhat higher than the pressure taken during sleep or immediately after awaking or prolonged rest. The latter is known as basal blood pressure. The so-called casual, or habitual, blood pressure is the sum of the basal blood pressure plus a supplementary increase caused by the usual physical and mental activity during waking hours.[19] The more strenuous the activity or emotional excitement preceding the examination, the higher will be the supplementary increase and herewith the habitual blood pressure. It will be higher in a nervous, hyperirritable person. Hence, frequently a marked difference of the blood pressure readings at the first consultation of an apprehensive person and at a later examination. This is a well-known fact, though not always appreciated in the evaluation of therapeutic trials.

1. The Level of Basal or Habitual Blood Pressure is No Indicator of Future Hypertension

The habitual blood pressure of healthy normal persons varies greatly. A person with a habitual blood pressure of 145/95 may be healthy and remain so just as well as one with a blood pressure of 90/60. Both, however, may become victims of progressive essential hypertension. Chinese are known to have a considerably lower habitual blood pressure than Caucasians. It is remarkable that Chinese may present all the manifestations of essential hypertension including hypertrophy of the heart, ocular changes, and apoplectic strokes at a blood pressure as relatively low as 130-140/85-90.[5]

The blood pressure of certain animals is physiologically very high as compared with humans. In the femoral artery of dogs the systolic blood pressure was found to be 110 mm. of Hg; in the tail of a rat, 106; of a mouse, even 136 mm. of Hg. A condition comparable to essential hypertension of man, however, is not known to occur in animals. It would be recognized by hypertrophy of the heart, which is found if hypertension is experimentally produced by tightening of the renal artery. This was observed first by Lewinski,[6] in 1880, and much later by a host of investigators following Goldblatt's technique. Dr. Rankin McIntyre, a veterinarian with large experience, informed me that spontaneous cardiac hypertrophy in dogs is only found as result of interstitial nephritis.

2. Degree of Supplementary Blood Pressure Not Necessarily Indicative of Future Essential Hypertension

Persons who lived for many years under most active stress and strain need not become hypertensives. Competitors at Olympic games are not known to be candidates of essential hypertension. The same holds true for those who had experienced the

most horrible emotional turmoils in concentration camps. An unbiased clinician will find many of the interpretations of essential hypertension by psychologists and "psychosomaticists" naïve, to put it mildly. Recently I was impressed by the normal blood pressure of a veteran who had been captured on Bataan and tortured in a Japanese concentration camp, where he had suffered from malaria and dysentery, who had been divorced by his wife after his return home, and had lost his child and his job. The counterpart is the American Negro, who is known to become victim of essential hypertension with particular frequency. For the great majority of these Negroes there was no reason for unusual supplementary blood pressure increase, neither physically nor emotionally.

3. Essential Hypertension Develops if the Homeostatic Mechanism of Blood Pressure Is at Fault

According to the preceding paragraphs this concept implies the failure of proper cooperation and coordination of many organs and functions. It requires a holistic aspect of a person. What are the proofs?

It is a well-known fact that persons with essential hypertension are hyperreactors to vasopressor stimuli. Their supplementary blood pressure is therefore a larger fraction of the habitual pressure than in normal persons. Such pressure stimuli are physical exercise, intense cold, epinephrine injections, cigarette smoking, emotional excitement, and the like. Essential hypertensives, however, are also hyperreactors to vasodilating stimuli. Acetyl-β-methylcholine injected into essential hypertensives lowers their systolic and diastolic blood pressure three to four times more than it lowers the blood pressure of normals.[7] Six patients whose blood pressure under resting conditions has decreased to a normal level at the time of injection showed, nevertheless, definitely greater percentile decrease in blood pressure than did nonhypertensive persons. It therefore seems clear that the greater response to vasodilating stimuli is independent of the basal level of blood pressure and is probably related to the "hypertensive disease."[7]

The investigators of the Mayo Clinic commented on their findings as follows: "It is difficult to understand how peripheral blood vessels which display a hyperdilatation in response to the administration of choline derivatives can be maintained in a state of increased tone in the case of hypertensive individuals, unless we assume that the concentration of acetylcholine at nerve-endings of the cholinergic vasodilator nerves of these patients is subnormal." There is no evidence of such a deficiency. It is interesting that dogs with artificial hypertension produced by Goldblatt's method did not show hyperreaction to acetyl-β-methylcholine, which suggests a different mechanism operative in essential hypertension than in renal hypertension.

In 1932 we studied the effect of moderate physical exercise on the blood pressure of hypertensives as compared with normals.[8] Not only was the elevation of systolic blood pressure usually much greater in hypertensives, but from 2 to 12 minutes after the exercise the blood pressure often fell below the original level more than in normals. In some of the hypertensives the diastolic pressure also dropped to a lower level than in normals after the exercise. From these observations we concluded that the blood pressure is more labile in hypertensives than in normals. In other words, the homeostasis of blood pressure in essential hypertensives is less efficient.

More strenuous physical exercise has been found to raise the systolic but to lower the diastolic pressure in most juvenile hypertensives.[9] This indicates an effect of epinephrine as was first described by the present author in 1912.[10] Recent studies on young men drafted for military service in Holland revealed the following results. In some mild hypertensives doing normal work the elevated blood pressure did not return to its rest level even after several hours. Excessive rising of both systolic and diastolic pressure was seen in others.

In a group of labile hypertensives muscular exercise was followed by considerable drop of both systolic and diastolic pressure far below the original level observed before the exercise.[20]

In their studies on the "cold pressor test," Hines and Brown [11] emphasize "some delay in the return of the blood pressure to the previous basal level" in hypertensive hyperreactors as compared with normals. In this test always both systolic and diastolic pressure rise, suggesting a reflex mechanism without involvement of epinephrine.

Our statement that the mechanism of the blood pressure homeostasis comprises more than the activity of one organ, particularly of the vasomotor centers only, is corroborated also by the common finding of diffuse hyperplasia and adenoma formation of the adrenal cortex in essential hypertension. These changes of the adrenals, however, are not the cause of essential hypertension, even if some hirsutism and low sodium chloride concentration in sweat point toward hyperactivity of the adrenal cortex.[12] Almost total bilateral adrenalectomy carried out in a case of essential hypertension caused no eventual change in the level of blood pressure. Thorn and his group also emphasize that complete bilateral adrenalectomy in severely hypertensive patients does not necessarily decrease the level of basal blood pressure, in spite of increased excretion of sodium and chloride.[13] The adrenals are only intercalated in the homeostatic device regulating the blood pressure.

The same holds true for the role of the blood pressure restrainers in the carotid sinus and depressor nerves. It has been demonstrated that the function of these moderator nerves is not abolished or even diminished in essential hypertension. There can hardly be any doubt that they participate in the regulation of blood pressure, but their insufficiency cannot be the cause of essential hypertension.[14]

What Causes a Failure of Homeostasis of Blood Pressure?

All homeostatic mechanisms developed gradually during phylogenetic evolution. Different environments required different adaptations in order to maintain a stable state of the body and to survive. "Lower animals, which have not yet achieved the degree of control of stabilization seen in the more highly evolved forms, are limited in their activities and handicapped in the struggle for existence" (W. Cannon [15]). The gradual evolution of lower animals to the highest level of human beings required adaptations and improvements of "the wisdom of the body" in order to maintain the *milieu intérieur* stabilized. With the evolution from quadrupeds into bipeds a new strain was imposed on the homeostatic mechanism of the blood pressure. The disturbing influence of gravity on the blood flow had to be overcome. It is well known that a domesticated rabbit held in vertical tail-down position for any length of time gradually passes into a shock-like condition and may die within 20 to 30 minutes from "gravity shock" due to stagnation of blood in the splanchnic vessels and consequent inadequate diastolic filling of the heart. It seems that in orthostatic hypotension of certain asthenic persons with flabby abdominal muscles, they have not achieved sufficient homeostasis of the blood pressure which protects normal persons from the influence of gravity. As a matter of fact, the same disturbance of homeostasis can also be produced by acquired lesions or chemical paralysis of the sympathetic vasoconstrictors.

Nervous, hyperirritable, emotional persons are more often than others exposed to situations producing greater elevation of supplementary blood pressure. Modern conditions of life and business in particular bring about situations of this kind with greater frequency. But only those persons with somewhat insufficient homeostasis of blood pressure will be unable to withstand this strain and will become victims of essential hypertension.

Cannon pointed out that homeostatic mechanisms quite generally are liable to senile deterioration. Hence the mild rising of habitual blood pressure with advancing age.[8] It is understandable that failure of homeostasis will eventually result in elevation rather than in lowering of blood pressure, because a human being is much more often exposed to vasoconstrictor than to vasodilator stimuli.

The main etiologic factor of essential hypertension which outweighs the influence of climate, nutrition, occupation, smoking, and other environmental influences is heredity. It is unnecessary to repeat here all the conclusive investigations—statistical studies and investigations on twins and on healthy family members of hypertensive persons who may be recognized as candidates for future essential hypertension. There appears to be almost unanimity on this point. Most careful studies carried out by Weitz were suggestive but not conclusive of a dominant Mendelian type of heredity. Can we subscribe to this interpretation on the basis of the preceding discussion?

The homeostatic mechanism of blood pressure is an attribute of higher organized animals. Its presence is entirely independent of sexual mating. It cannot, therefore, depend on one or a few genes but it rather depends on the potential power of development of a fertilized ovum as a whole, that is, on the sum total of genes which are the carriers of life itself. Only the precision and the pace of decline of homeostasis, not its presence, can be subject to hereditary variations and be influenced by sexual mating. With this integrative, holistic concept in mind, we must place homeostasis of blood pressure in the category of what the biologists call "continuous variability." It applies likewise to many human traits, such as height, head shape, other body proportions, mental capacity, or the physiologic—that is, undisturbed by environmental factors—span of life. This continuous variability is the basis of racial variability and "probably the most important in evolution" (Dobzhansky[16]). Continuous variability implies multifactorial, polygenic heredity and thus almost precludes the possibility of further unravelling the type of Mendelian heredity. Gradual differences of precision and decline rather than sharp limits between normal and abnormal characterize constitutional disorders of homeostasis. For these reasons any efforts to determine the exact mode of hereditary transmission have been and will be very difficult if not futile.

One conclusion emerges, however, from these considerations. Essential hypertension occurs on the basis of a weakly developed, insufficiently working, and exhaustible homeostasis of blood pressure. Its etiology is genetic in nature, although liable to modifications by environmental factors. It is reasonable and preferable to substitute the term constitutional hypertension for the term essential hypertension because it eliminates the connotation of unjustified ignorance and designates clearly the nature of this type of hypertension as contrasted with the various types of symptomatic hypertension.

Now we may answer the question of an editorial in the *Lancet*: "Is Hypertension a Disease?"[17] Certainly not of its own. It is a sign of very different significance. It may be one of the manifestations of an organic disease of various organs. This we call symptomatic hypertension. Or it can occur primarily without structural basis as constitutional (essential) hypertension. If such a constitutional elevation of blood pressure exists without producing any symptoms or secondary anatomical changes, it cannot well be called a disease, indeed. It is merely a definite constitutional predisposition to a disease which usually but not necessarily develops on this basis after a variable length of time. It is unnecessary to elaborate on symptoms and signs of this well-known disease. Arterial hypertension of long standing leads to hypertrophy and later to dilatation of the heart, with potential insufficiency of the overstrained heart and subsequent congestive heart failure (hypertensive heart disease). It leads likewise to compensatory proliferative changes in the

wall of small arteries, known as arteriolosclerosis, which, in turn, raises the elevated blood pressure even more and thus establishes a vicious circle. Involvement of retinal, cerebral, and, particularly, renal arteries determines the clinical picture and course of hypertensive vascular disease.

The vascular changes in hypertensive persons may develop rapidly or very slowly. They do not parallel the degree of hypertension and depend on the individual susceptibility of the person and his vessels. Some authors believe that the vascular changes and constitutional hypertension stem from a common primary defect responsible for both. Increased pressure upon the vessel wall from within as an inciting factor of thickening of the wall, however, must be considered as fact. It is only a special variety of a more general principle. Increased inside pressure produces thickening in all elastic, contractile hollow tubular structures, as in the intestines, stomach, or urinary tract. Intensity and rapidity of development of these arteriolar changes, and tendency to hyaline degeneration and necrosis of the arteriolar wall determine the course of the disease. There are, in my opinion, only gradual differences between all these varieties of the disease, from the benign, many-year-long type with little or no symptoms to the malignant, rapidly fatal variety.

One very important point requires emphasis. Any most benign type of constitutional hypertension may become an iatrogenic disease. Symptoms, such as headache, dizziness, respiratory embarrassment, or chest pain, are often provoked by the first information about the elevated blood pressure of a hitherto perfectly healthy and asymptomatic person. If this information is unavoidable, it should always be accompanied by reassurance of the person (not yet a "patient") and by careful instruction concerning the significance of the finding. To mention the unwarranted possibility of a malignant course is a psychological crime. Nobody can foresee the course of constitutional hypertension without observation of the person for a longer period of time. This type of iatrogenic disease is of course a psychoneurosis of a blood-pressure-conscious person and due not to hypertension but unfortunately to medical consultation.

We must take exception to the opinion of the British cardiologists who hesitate to recognize essential hypertension as "a specific clinical entity."[3] What else should it be called? It is a well-defined constitutional predisposition to a well-defined specific disease that may or may not develop and may or may not shorten the life span of its carrier within an often unpredictable period of time.

Management of Constitutional Hypertension

What may be inferred from the concept of constitutional hypertension with regard to its management? As long as constitutional hypertension is merely a predisposition and not or not yet an actual disease it is an object of prevention rather than of treatment. Anything producing excessive elevation of supplementary blood pressure should be avoided or restricted. In the first place, "peace of mind" should be restored as far as possible, periods of rest should be advised, excessive cigarette smoking eliminated. Thirty to sixty minutes of resting in horizontal position—if possible with a little dozing off—before or after lunch time should become routine. Frequent vacations of a few days are preferable to prolonged vacations once a year. Sufficient sleep should be provided if necessary. Small amounts of phenobarbital—¼ to ½ grain (15 to 30 mg.) at bedtime only—may be sufficient for this purpose.* Excessive amounts of salt in the diet should be avoided. To achieve "peace of mind" may often be difficult. It does not require, as a rule, the aid of a psychiatrist. Knowledge of human nature, common sense,

*One of the Rauwolfia serpentina preparations usually reduces the asymptomatic elevated blood pressure very well and is particularly valuable in such cases.

and tactful, sympathetic discussion of the individual problems is all that is necessary. The danger of creating an iatrogenic blood-pressure-conscious hypochondriac should constantly be remembered.

Treatment becomes necessary if constitutional hypertension actually has led to a disease, if symptoms referable to hypertension are complained of, or if evidence of heart strain or arteriolosclerotic changes is present. It is not within the scope of this discussion to elaborate on details of treatment of hypertensive vascular disease. It suffices to emphasize a few principles of the treatment. It is not necessary and not enough to be familiar with the large armamentarium of drugs and various therapeutic methods at our disposal. It is sheer waste of one's cerebral faculties to remember all the names of proprietary preparations containing the same therapeutic principle. What is needed is the proper choice of therapeutic measures, appropriate to the individual patient and based on experience and knowledge of the pharmacologic principles, of undesirable side-effects, and even of dangers of certain procedures. There is no routine treatment of hypertensive vascular disease.

Rauwolfia serpentina, for instance, given as reserpine (Serpasil, Ciba Pharmaceutical Products, Inc.) or another proprietary preparation, combines a mild sedative with a hypotensive effect probably by action upon the hypothalamus and other cerebral centers. It regularly slows down the pulse rate, which is particularly valuable in patients with nervous sinus tachycardia often associated with constitutional hypertension. As it is mostly well tolerated and without significant toxic side-effects, it is good practice to use it before more potent drugs are given a trial. Lowering of a moderately elevated blood pressure often does not occur before two to three weeks. In advanced cases it usually is ineffective.

Hydralazine (Apresoline) increases the renal blood flow, but it also produces tachycardia and increased cardiac output. This implies increased heart work, which may precipitate failure of an overstrained heart. It was indicated, for instance, in the case of a Negro woman with a blood pressure of 260/140, retinal changes, and advanced renal impairment (N. P. N. 140 mg. per 100 cc.) but no evidence of cardiac damage except for hypertrophy of the left ventricle.

In advanced cases it is advisable to look for the special danger point. Is it the kidney as in the just mentioned case, or is it the heart or the brain? One should never forget that it is not the blood pressure but the patient as a whole who is to be treated. Apparently "successful" considerable lowering of high blood pressure achieved by any method may reduce the blood flow through vital organs and even precipitate renal failure or thrombosis both of the coronary and of the cerebral vessels. Myocardial infarction which brings about marked "improvement" of high blood pressure is not uncommonly followed by cerebral thrombosis. The presence of atherosclerosis accompanying constitutional hypertension should be appreciated. It is a warning with regard to a possible cerebrovascular accident. It must be suspected if the elevated diastolic pressure shows a spontaneous gradual decrease with resulting increase of pulse pressure.

There is no question that severe and otherwise refractory cases of constitutional hypertension with its organic consequences can be much improved by hexamethonium and similar blocking agents. This treatment, however, requires initial hospitalization and thorough instruction of the patients to take their own blood pressure and adjust the injected doses of hexamethonium accordingly. Some of the patients of the Mayo Clinic are instructed to take their blood pressure seven times per day.[18] It stands to reason that this treatment must be reserved for very severe cases who are and should be blood-pressure-conscious. Hexamethonium acts by blocking the autonomic ganglia, chiefly the sympathetic but also the parasympathetic ones. Hence the undesirable side-effects: not only orthostatic hypotension must be expected but also

visual accommodation, intestinal peristalsis, and urination may be impaired.

Sympathectomy differs from hexamethonium therapy by eliminating only the vasoconstrictors without interfering with the parasympathetic. I am in full accord with Proger, who would prefer a limited sympathectomy to continuous use of such potent hypotensive drugs which require lifelong careful supervision and involve dangers and ill effects that can occur from such drug treatment. It is true that cerebral hemorrhage, left ventricular failure, and deterioration of vision may be prevented by drastic lowering of the blood pressure. The potential danger of renal failure or coronary and cerebral thrombosis, however, has been mentioned previously. Nevertheless, it is a remarkable achievement if 90% mortality in two years has been reduced to about 50% by sympathectomy of those malignant cases.

Bilateral adrenalectomy is a heroic, a formidable treatment, which certainly should be considered only in exceptional, hopeless malignant cases. Neither sympathectomy nor adrenalectomy warrant the expected result. Not always is a lowering of blood pressure achieved by these surgical procedures. This experience demonstrates again that constitutional hypertension with its consequences is not simply due to increased vasoconstrictor tonus. It is a highly complex disorder of homeostasis which is not amenable to actual cure, only to slowing down and often prevention of its evil consequences by attacking certain links of the whole chain of factors which are concerned with the maintenance of normal blood pressure.

Summary

Permanent arterial hypertension may be symptomatic hypertension, that is, manifestation of an organic disease of the kidneys, endocrine system, nervous system, or peripheral vascular system, or it may be essential hypertension, which cannot be referred to any structural disease of a particular organ.

Casual, or habitual, blood pressure is the sum of basal blood pressure in absolute rest and supplementary blood pressure caused by physical and mental activity during waking hours.

The level of both basal and habitual blood pressure varies greatly both individually and racially but is no indicator of future essential hypertension.

The degree of supplementary blood pressure increases with the degree of nervous and emotional irritability. It is not necessarily an indicator of future essential hypertension.

Essential hypertension develops only if the homeostasis mechanism of blood pressure is at fault, whether the basal and supplementary blood pressure are individually high or low within the range of normality.

Many facts are suggestive of insufficient homeostasis of blood pressure in persons with essential hypertension.

The etiology of insufficient homeostasis of blood pressure is heredity. This makes the precise term "constitutional hypertension" preferable to the term "essential hypertension" because it avoids the unjustified connotation of our ignorance.

There is reason to assume that constitutional hypertension is not caused by one or two abnormal genes but that it belongs to the category of "continuous variability" which implies multifactorial, polygenic heredity because of the very complex nature of the homeostatic mechanism of blood pressure.

Constitutional hypertension is not a disease per se; it is merely a definite constitutional predisposition to disease which may or may not develop on this basis with or without the cooperation of extrinsic (environmental) etiologic factors. Hypertensive heart disease and hypertensive vascular disease may emerge from the predisposing constitutional hypertension.

This clarification of the situation is of value for the management of individual cases. Constitutional hypertension per se is only object of preventive measures with regard to potential disease. Treatment of

hypertensive disease requires consideration of the special danger points: heart, kidneys, eyes, and brain.

Not the high blood pressure but the patient with high blood pressure as a whole must be taken care of. The choice of the various hypotensive drugs, of dietetic restrictions, or of surgical procedures depends on careful study of the individual case.

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REFERENCES

1. Fishberg, A. M.: Hypertension and Nephritis, Ed. 5, Philadelphia, Lea & Febiger, 1954.

2. Schroeder, H. A.: Hypertensive Diseases: Causes and Control, Philadelphia, Lea & Febiger, 1953.

3. Hamilton, M.; Pickering, G. W.; Fraser Roberts, J. A. F., and Sowry, G. S. C.: The Ætiology of Essential Hypertension: 4. The Role of Inheritance, Clin. Sc. 13:273-304, 1954.

4. Griffiths, W. J., Jr., and Gallagher, T. J.: Differential Dietary Choices of Albino Rats Occasioned by Swimming, Science 118:780, 1953.

5. Snapper, I.: Chinese Lessons to Western Medicine: A Contributon to Geographical Medicine from the Clinics of Peiping Union Medical College, New York, Interscience Publishers, Inc., 1941.

6. Lewinski: Über den Zusammenhang zwischen Nierenschrumpfung und Herzhypertrophie, Ztschr. klin. Med. 1:561-582, 1880.

7. Engle, D. E., and Binger, M. W.: The Blood Pressure Response of Hypertensive Patients to Acetyl-Betamethylcholine, Proc. Staff Meet. Mayo Clin. 14:341-343, 1939.

8. Bauer, J., and Neuburger, F.: Die Blutdruckreaktion auf körperliche Arbeit bei abnormem Blutdruck, Ztschr. klin. Med. 120:628-633, 1932.

9. Tsuji, K.: Über die Pathogenese der essentiellen Hypertonie, besonders vom klinischen und pathologisch-anatomischen Standpunkte aus, Acta scholae med. univ. imp. Kioto 22:581-682, 1938.

10. Bauer, J.: Zur Funktionsprüfung des vegetativen Nervensystems, Deutsch. Arch. klin. Med. 107:39-102, 1912.

11. Hines, E. A., Jr., and Brown, G. E.: The Cold Pressure Test for Measuring the Reactibility of the Blood Pressure: Data Concerning 571 Normal and Hypertensive Subjects, Am. Heart J. 11: 1-9, 1936.

12. Schroeder, H. A., and Davies, D. F.: Studies on "Essential" Hypertension: V. An Endocrine Hypertensive Syndrome, Ann. Int. Med. 40:516-539, 1954.

13. Thorn, G. W.; Harrison, J. H.; Merrill, J. P.; Criscitiello, M. G.; Frawley, T. F., and Finkenstaedt, J. T.: Clinical Studies on Bilateral Complete Adrenalectomy in Patients with Severe Hypertensive Vascular Disease, Ann. Int. Med. 37:972-1005, 1952.

14. Bauer, J.: Essential Hypertension, Its Nature and Etiology, Acta med. scandinav. 108:18-36, 1941.

15. Cannon, W. B.: The Wisdom of the Body, Ed. 2, New York, W. W. Norton & Company, Inc., 1939.

16. Dobzhansky, T. G.: Genetics and the Origin of Species, Ed. 3, New York, Columbia University Press, 1951.

17. Is Hypertension a Disease? Leading Articles, Lancet 1:1224, 1954.

18. Allen, E. V.; Barker, N. W.; Hines, E. A., Jr.; Kvale, W. F.; Shick, R .M.; Gifford, R. W., Jr., and Estes, J. E., Jr.: Medical Treatment of Essential Hypertension, Proc. Staff. Meet. Mayo Clin. 29:459-478, 1954.

19. Smirk, F. H.: Pathogenesis of Essential Hypertension, Brit. M. J. 1:791-799, 1949.

20. Koster, L.; Alers, C. J.; van Ham, E. H., and van Westreenen, E.: Reactions to Heavy Muscular Exertion in the Analysis of Physical Insufficiency Syndromes, Acta med. scandinav. 149: 109-118, 1954.

Cerebral Hemodynamics and Metabolism in Accidental Hypothermia

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The use of hypothermia to protect the central nervous system from circulatory insufficiency has become of increasing importance in medicine. This report is concerned with studies of the effects of accidental hypothermia on cerebral hemodynamics and metabolism of two patients, one having a body temperature of 21 C (69.8 F) and the other, of 29.4 C (84.9).

Report of Cases

CASE 1.—A 58-year-old man, who was found by the police in an unfurnished, unheated room, was admitted to the District of Columbia General Hospital in a confused and disoriented state on Feb. 23, 1956. The patient was unable to relate a history of preceding events upon admission or after recovery. The duration of exposure was undetermined. He denied any alcohol or drug consumption.

On admission, the patient was shivering and lethargic but reacted to auditory and noxious stimulation. The blood pressure was 105/80 mm. of Hg; the pulse rate, 70 per minute, and the respiratory rate, 22 per minute. The rectal temperature, measured by means of a Tele-thermometer thermocouple, was 29.4 C. No other abnormal physical findings were noted.

Routine laboratory data, as well as serum electrolytes and liver function studies, were within normal limits. The chest x-ray was within normal limits. The electrocardiogram, taken at a rectal temperature of 29.4 C, revealed a normal sinus rhythm at a rate of 72 per minute, with moderate ST segment elevation in precordial leads V_4 through V_6. The patient's temperature was permitted to rise spontaneously, and by the second hospital day it had reached 38 C (100.4 F) rectally. He became afebrile on the fourth hospital day and made an uneventful recovery.

CASE 2.—A 43-year-old man was admitted to the District of Columbia General Hospital in a comatose state on Jan. 17, 1956. He had been found lying in a shallow pond. The environmental temperature was approximately −1 C. The duration of exposure could not be determined; the patient subsequently could recall only that he had been drinking a large quantity of wine. The past medical history was not pertinent.

Neither blood pressure nor peripheral pulse could be obtained on admission. The respiratory rate was 9 per minute. The rectal temperature, measured by means of a Tele-thermometer thermocouple, was 21.6 C (70.9 F). The patient was completely unresponsive and appeared moribund. The skin was extremely cold to touch, and erythema was noted about the toes. The extremities were stiff, and the knees were flexed. The lungs were clear and heart sounds distant; the apical rate was 35 per minute, and no murmurs were heard. The liver was palpable 3 cm. below the right costal margin. The deep tendon reflexes were hypoactive but equal, and no neurological abnormalities were elicited.

Routine laboratory data on admission, serum electrolyte values, and hepatic function tests obtained during the hospital course were all within normal limits. A lumbar puncture performed on the second hospital day demonstrated no abnormalities. Roentgenograms of the skull and chest were normal. An electrocardiogram, taken when the rectal temperature was 22 C (71.6 F), revealed a sinus bradycardia of 36 per minute, with marked ST elevation and T wave inversion in precordial leads V_2 through V_6. A repeat tracing at a rectal temperature of 38 C revealed only sinus tachycardia.

The patient was allowed to warm in a room-temperature environment without the application of additional heat. At a rectal temperature of 32 C (89.6 F), nine hours following admission, the patient regained consciousness, muscle stiffness disappeared, and voluntary movement returned. His rectal temperature continued to rise until 48 hours following admission, when it reached a maximum of 41 C (105.8 F). Symptomatic measures proved

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*Cerebral Blood Flow Studies During and After Hypothermia**

Case No.	Age, Yr.	Temp. Degrees C (F)	CBF	$CMRO_2$	CVR	MAP
1	58	30.0 (86.0)	30.8	1.6	3.5	108
		37.8 (100.0)	54.2	2.3	1.6	85
2	43	23.0 (73.4)	30.9	1.5	2.8	86
		39.7 (103.4)	43.8	2.6	1.6	69
		37.2 (99.0)	43.3	2.4	2.3	98

*CBF signifies cerebral blood flow in cc./min./100 gm. of brain; $CMRO_2$, cerebral oxygen consumption in cc./min./100 gm. of brain; CVR, cerebral vascular resistance in mm. of Hg/cc. of blood/min./100 gm. of brain; MAP, mean arterial blood pressure in mm. of Hg

adequate to control the hyperthermia, and the patient made an uneventful recovery.

Cerebral hemodynamic and metabolic studies determined on both patients immediately on admission and during the recovery period are presented in the Table. In both patients there was a decrease in the rate of cerebral blood flow and cerebral oxygen utilization, an increase of cerebral vascular resistance, and no change in mean arterial pressure with a reduction of body temperature.

Scheinberg and Stead's modification[3] of the Kety and Schmidt procedure[2] for the determination of cerebral blood flow was applied in this study. The gas mixtures utilized were those described by Kety.[2] Blood oxygen was determined by the manometric technique of Van Slyke and Neill.[4] Mean arterial blood pressure was obtained directly from the femoral artery by means of a damped aneroid manometer.[4]

Comment

Previous reports dealing with the effects of induced hypothermia on cerebral hemodynamics and metabolism have been difficult to evaluate because of the possible influence of drugs administered concomitantly. Albert and Fazekas[5] recently reported the effects of induced hypothermia on cerebral hemodynamics in five patients. They observed a moderate to marked reduction in cerebral blood flow and cerebral metabolism, an increase in the cerebral vascular resistance, and a reduction of mean arterial pressure. The induction of hypothermia in their studies included the use of thiopental (Pentothal) sodium, trimethaphan camphorsulfonate (Arfonad), and chlorpromazine.

The only apparent factor in the present study, other than the accidental hypothermia which may have influenced the findings was the unknown amount of alcohol ingested by Patient 2. Previous reports on the effects of alcohol upon cerebral hemodynamics and metabolism[6] have failed to demonstrate any significant change with concentrations of blood alcohol as high as 200 mg. per 100 cc.

In the present study, the cerebral blood flow was found to be reduced in both patients while hypothermic. Since there was no decrease in mean arterial pressure in either patient, and since repeated studies when the body temperature had been normal revealed relatively normal rates for cerebral blood flow, it would seem that the reduction of cerebral blood flow was produced by increased vascular resistance due directly to the hypothermia. The marked increase in cerebral vascular resistance in both patients during hypothermia is difficult to explain in view of the normal mean arterial pressure. Similar results have previously been reported during induced hypothermia in spite of a decreased mean arterial pressure.[5] An increased blood viscosity due to hypothermia, or actual cerebral vasoconstriction, may play a role in the increased cerebral vascular resistance. However, the exact mechanism remains obscure.

In both subjects hypothermia was associated with a marked reduction in cerebral oxygen consumption as compared to values observed when body temperatures had returned to approximately normal values. Although similar reduction in cerebral blood flow accompanied this change, the circulatory alterations could hardly have been responsible, since oxygen delivery remained adequate to support even a normal cerebral metabolism. Undoubtedly the reduction in cerebral oxygen consumption can be attributed entirely to the known effects of hypo-

thermia in reducing all enzymatic activity and cellular metabolic requirements. It should also be noted that there was not found in these two cases a directly proportional relationship between body temperature and reduction in cerebral metabolic rate. It is possible that some constant relationship exists, although it may not be a simple one. It could easily be obscured by relative inaccuracy of measurement in the procedure used or by individual variations among different subjects.

It is of interest to note that both patients demonstrated a hyperthermic rebound after their initial marked decrease in body temperature. The patient who suffered the greatest reduction of body temperature responded with the more marked hyperpyrexia. Extremes of temperature have often been noted to affect adversely the temperature-regulating mechanism of the body.

Summary

Two cases of marked accidental hypothermia are presented. Studies of cerebral hemodynamics and metabolism during hypothermia and after recovery revealed an initial reduction in cerebral blood flow, cerebral oxygen consumption, and cerebral oxygen delivery. There was an increase in cerebral vascular resistance in spite of normal mean arterial blood pressure. It is probable that the reduced cerebral oxygen consumption was due to the reduction in body temperature.

Although in one case the temperature was recorded as low as 21 C, no tissue damage was noted. Comparison of results during and after hypothermia reveals no permanent deterioration in cerebral hemodynamics and metabolism.

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REFERENCES

1. Scheinberg, P., and Stead, E. A., Jr.: The Cerebral Blood Flow in Male Subjects as Measured by the Nitrous Oxide Technique: Normal Values for Blood Flow, Oxygen Utilization, Glucose Utilization, and Peripheral Resistance, with Observations on Effect of Tilting and Anxiety, J. Clin. Invest. 28:1163, 1949.

2. Kety, S. S., and Schmidt, C. F.: The Nitrous Oxide Method for the Quantitative Determination of Cerebral Blood Flow in Man: Theory, Procedure and Normal Values, J. Clin. Invest. 27:476, 1948.

3. Peters, J. P., and Van Slyke, D. D.: Quantitative Clinical Chemistry: Methods, Baltimore, Williams & Wilkins Company, 1932, Vol. 2, p. 321.

4. Alman, R. W., and Fazekas, J. F.: Apparatus for Continuous Blood-Pressure Observation, New England J. Med. 248:105, 1953.

5. Albert, S. N., and Fazekas, J. F.: Cerebral Hemodynamics and Metabolism During Induced Hypothermia, Current Res. in Anesth. & Analg., to be published.

6. Battey, L. L.; Heyman, A., and Patterson, J. L., Jr.: Effects of Ethyl Alcohol on Cerebral Blood Flow and Metabolism, J. A. M. A. 152:6, 1953.

A Long-Term Follow-Up of Nontoxic Nodular Goiter

Effect of Clinical Selection on the Observed Incidence of Malignancy

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There has been a great deal of controversy in recent years over the management of nontoxic nodular goiter. Many authorities have insisted that all such goiters should be extirpated because of the risk that they are, or might become, malignant.[1-4] Some of them have claimed that as many as 15% of nontoxic nodular goiters are malignant.[3,4] Others have pointed out that thyroid cancer is a rare disease, while nodular goiter is fairly common, and that figures such as the above, which are based on highly selected surgical statistics, are not applicable to the population as a whole.[5-8] The true prevalence of malignancy in nontoxic nodular goiter has been estimated by these authors to be considerably less than 1%. Several authorities have concluded that routine removal of all nontoxic nodular goiters is not indicated, and would in fact cause a surgical morbidity and mortality which would outweigh the additional cures of thyroid cancer that might be obtained.[5,8,9]

One of the crucial points in this controversy is the question of whether it is possible to differentiate clinically between benign and malignant goiters. Most authorities would agree that if this could be done with sufficient accuracy routine extirpation of all goiters would be contraindicated. It is often stated, however, that such differentiation is impossible, except in the case of far-advanced carcinomas where there is little hope for cure. The fact that the majority of curable thyroid cancers are operated on under the diagnosis of benign goiter is cited as evidence that clinical differentiation at an early stage is impossible. However, failure to make the diagnosis of cancer preoperatively is not at all equivalent to failure to suspect cancer and to recommend surgery. After all, these "apparently benign" glands were selected for surgery from a much larger group of clinically benign goiters.

Calculations of the incidence of malignancy among unselected nodular goiters have of necessity been indirect. A study which will yield direct evidence on this point has been initiated in a New England community[10]; unfortunately, it will be many years before conclusive results are available. Similarly, the evidence that "dangerous" goiters can be distinguished clinically from "nondangerous" ones is largely indirect. Some direct evidence on this point is available,[3,8] but no definitive study with an adequate follow-up period has yet been reported. It seemed desirable, therefore, to attempt such a study, using the clinical material of the Grace-New Haven Community Hospital.

Clinical Material

New Haven is in a nongoitrous area. However, a significant number of the residents of this area were born in goitrous regions of Europe. Thus the population is partly "goitrous" and perhaps can represent an average United States population in this respect. The Grace-New Haven Community Hospital is a general hospital, providing primary hospital care to a fairly stable population in New Haven and surrounding Connecticut communities. A considerable number of referrals from other institutions are also seen, but few of these are from distant areas. There has never been any official hospital policy on the treatment of nodular goiter. During most of the period covered

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by this study, the prevailing attitude among the staff was that only a minority of patients with nontoxic nodular goiter needed surgical treatment. The experience at this hospital can serve very well, therefore, for an evaluation of preoperative selection in nontoxic nodular goiter.

The records of inpatients listed in the record-room diagnostic index as having nodular goiter or thyroid cancer between 1921 and 1945 were reviewed. Patients were divided into three categories, as follows:

I. Patients Not Operated on Within Six Months of Official Diagnosis of Nontoxic Nodular Goiter

This group was arbitrarily deemed to consist of patients in whom the risk of thyroid cancer had been considered negligible on clinical evaluation, regardless of the reason for failure to operate. Unfortunately, the number of patients in this category is not nearly as large as it should be. The great majority of the patients found to have nodular thyroids in the course of an admission for some other condition are not listed in the diagnostic index under the heading of goiter.

II. Patients Who Received Minimal Surgical Treatment

Minimal surgical treatment in this instance means excision of one or more thyroid nodules, without removing surrounding tissue. This group is considered separately because of the widely taught doctrine that such treatment of nodular goiter is inadequate—and, in fact, equivalent to no treatment. It was assumed that all of these goiters had been evaluated as benign. Presumably, in some, future malignant changes had been feared, and prophylactic adenomectomy was therefore performed. It was impossible to estimate the number of such cases, since the reason for adenomectomy was usually not stated.

III. Patients Who Received More Extensive Surgery

More extensive surgery included lobectomy and subtotal thyroidectomy. This was a heterogenous group. It included cases in which thyroidectomy was performed for cosmetic reasons, cases with pressure symptoms, and cases in which the goiter was suspected to be malignant. Patients with unequivocal preoperative diagnosis of thyroid cancer were excluded, however.

Some patients fell into more than one category. For example, a patient undergoing adenomectomy one year after diagnosis of nontoxic nodular goiter had been made and a subtotal thyroidectomy three years later would be included in all three categories.

Patients known to have cancer of the thyroid were not included in this series. This has been done by some authors discussing the problem of nontoxic nodular goiter,[1,3,4] although it obviously distorts the statistics. A clinical impression of thyroid cancer, unsupported by biopsy or by the demonstration of metastases, did not bar a patient from inclusion. Such impressions were wrong more often than they were right. When, however, the clinical impression of cancer was so strong that the operation scheduled was confirmatory biopsy rather than thyroidectomy, the case was excluded.

The year 1945 was chosen as the closing year for admission of patients to this study, so that at least a 10-year follow-up of living patients would be possible. Follow-up was accomplished in several ways. In many cases, patients proved to have been followed fairly closely for various reasons since admission to this series and to have records which were up to date as of 1954 or 1955. Patients in Categories I and II whose records were not up to date were traced through city directory entries and various other sources. Questionnaires were mailed to these patients to obtain information regarding treatment elsewhere, regression or recurrence of nodules, etc. Response to these questionnaires was good. Of the patients whose current addresses could be obtained, only 11 in Category I and 1 in Category II failed to reply. In the case of patients known or presumed to have died, inquiry was made at the appropriate vital

TABLE 1.—*Distribution of Patients by Category and Sex*

	Male	Female	Total
Category I (no surgery)	21	119	140
Category II (Adenomectomy)	8	72	80
Category III (more extensive surgery)	19	64	83
Duplications	2	5	7
Total patients	46	250	296

statistics agency regarding the cause of death. Follow-up of patients in Category III was less thorough. Special efforts to trace these patients was not made, since it is not the purpose of this study to evaluate thyroidectomy.

Table 1 gives the number of patients, by sex, in each category. The female : male ratio of 5 :1 is the same as that reported in recent clinical studies in goitrous [8] and non-goitrous [10] areas, but is over twice as high as the ratio found in autopsy studies.[11,12] There is no significant difference between the sex ratios of the operated-on and non-operated-on groups. Since the non-operated on-group is not a representative sample, however, no conclusions can be drawn from this.

Table 2 gives the clinical impressions regarding nodularity and the findings in the patients operated on. As in many other studies, the clinical impression was uninodular in most of the patients, but very many of these actually had multinodular goiter. In most of the Category II patients, operative exposure of the thyroid gland was quite limited and the surgeon did not palpate the entire gland. It is probable that more of these glands were multinodular than is indicated. In the Category III cases, where reasonably complete examination was the rule, the preoperative ratio in favor of uninodular glands was reversed postoperatively.

The difference in the incidence of malignancy between the uninodular and multinodular glands is not statistically significant.

Follow-Up Results

Of the 140 patients in Category I, 76% have been followed to death or to 1954-1955, and 24% were lost to follow-up prior to 1954. Forty per cent are known to be dead. The cause of death was determined in every case but one. Fifteen, or 11%, of these patients subsequently underwent thyroidectomy. In nine of these, the operation was performed within four years of the diagnosis. In the remainder, it was 7 to 11 years later.

At the end of the follow-up period, 75 of the Category I patients had persistent or recurrent goiter, 22 did not have goiter, and the status of the remaining 43 was unknown. Of the 22 known not to have goiter, 11 had undergone thyroidectomy, and in 11 the goiter had regressed spontaneously. Many of the latter were goiters which had appeared during pregnancy.

One patient of the one-hundred forty in this group was later found to have thyroid cancer.

CASE 1.—A 60-year-old Italian-born white woman was first seen at the New Haven Hospital in 1944, complaining of fatigue and a large goiter. Her first goiter had appeared soon after puberty. She had received iodine treatment for some years, without benefit. In 1934, after her husband's death, she developed nervousness and tremor and began to lose weight. Thyroidectomy was performed at another hospital, and the patient's symptoms were relieved. Pathological diagnosis was "cystic degeneration"; there was no suggestion of malignancy. (These slides were reviewed in the

TABLE 2.—*Number of Thyroid Nodules: Clinical Impressions and Operative Findings*

Category	Clinical Impression			Found	
	Uninodular	Multinodular	Diffuse or Uncertain	Uninodular	Multinodular
I	79	46	15	----	----
II Total	69	8	3	59	21
(malignant)	(2)			(2)	
III Total	55	22	6	33	50
(malignant)	(6)	(5)	(2)	(5)	(8)

Department of Pathology, Yale University.) In 1940, a lump appeared in the neck. This increased in size gradually up to the time of admission. In 1942 the patient received x-ray therapy to the neck. Between 1941 and 1944, the following symptoms developed: loss of hair, puffiness of the eyelids, sensitivity to cold, drowsiness, increasing fatigue. On examination at the New Haven Hospital in 1944, the patient was found to have sparse gray hair, coarse skin, large tongue, edema of the eyelids, and a large multinodular goiter. B. M. R. was −31%, and serum precipitable iodine was 1.3γ per 100 ml., confirming the clinical impression of myxedema. It was thought that this patient's goiter was probably malignant, and surgery was planned after the correction of the myxedema. The latter was accomplished in two months, and operation was then advised by the physician who was following the patient in the clinic. However, the patient refused surgery and did not return to the clinic for further observation. She was next seen in 1947, with a huge goiter and acute respiratory obstruction. Tracheotomy and partial thyroidectomy were performed. Pathological diagnosis was carcinoma. The patient continued to have respiratory obstruction and died as a mediastinal exploration was about to start. Permission for autopsy was not obtained.

Comment.—This patient probably had a malignant goiter in 1944, when she was first seen at the New Haven Hospital. She should have been persuaded to accept surgical treatment at that time.

Of the 80 patients in Category II, 73% have been followed to death or to 1954-1955, and 27% were lost to follow-up. Eighteen per cent are known to be dead. The cause of death was determined in each case. There were no operative deaths. Four of the patients underwent additional surgery 6 to 20 years after adenomectomy.

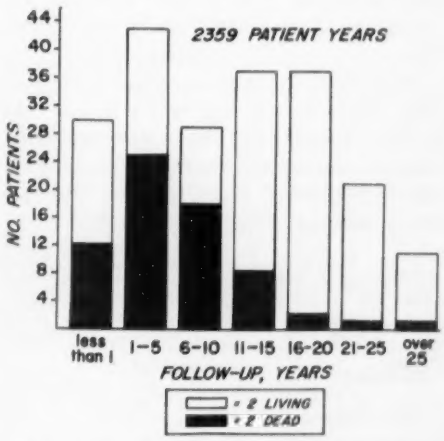
At the end of the follow-up period, 7 of the Category II patients had recurrent goiter, 55 did not have goiter, and the status of 18 was uncertain. In two patients of this group, the excised nodule proved to be malignant on microscopic examination. There have been no cases in which cancer developed subsequent to adenomectomy.

CASE 2.—A 60-year-old white woman was admitted to the New Haven Hospital in 1933, for treatment of a uninodular goiter. The nodule had appeared in 1913, when the patient was 40, and had changed little until six months prior to admission, when it began to grow progressively. The preoperative diagnosis was "thyroid adenoma." The adenoma was excised in 1933, and no additional therapy was given. Pathological diagnosis was carcinoma. The patient has had no recurrence. In 1952 she underwent mastectomy for a breast cancer. Diagnostic admission in 1955, when she was 82, uncovered no evidence of either thyroid or breast disease.

CASE 3.—A 49-year-old white woman was admitted to the New Haven Hospital in 1934, complaining of nervousness, low blood pressure, and weight loss. She was found to have a thyroid nodule 3 cm. in diameter. Hospital evaluation yielded no evidence of toxicity, and the nodule was excised under the preoperative diagnosis of "nontoxic adenoma." No additional therapy was given. Pathological diagnosis was papillary adenocarcinoma. She replied to a questionnaire in 1955 stating that she had had no recurrence up to that time.

Consolidating Categories I and II and eliminating duplications, the following figures are obtained: There were 218 patients who received none or minimal surgery during the first six months after diagnosis. Seventy-six per cent of them have been followed to death or to 1954-1955. Thirty-two per cent are known to be dead. The cause of death is known in every case except one. The total follow-up represents 2359 patient-years. The figure gives the distribution of these conservatively treated patients by years of follow-up.

Special follow-up efforts were not made for the patients in Category III. Only 46%



Follow-up of conservatively treated patients with nontoxic nodular goiter.

TABLE 3.—*Status at the End of Follow-Up of Twelve Category III Patients with Primary Thyroid Cancer*

Preoperative Diagnosis	No. Patients	Dead			Living, No Recurrence
		Postop.	Thyroid Cancer	Other Causes	
Benign	6	1		2	3
? Carcinoma	5	1	2	1	1
Carcinoma	1	1			
Total	12	3	2	3	4

of these have been followed to death or to 1954-1955. Half of them are dead. The cause of death is known in every case. There were three operative deaths, all in patients who proved to have thyroid cancer. Five of the eighty-three patients underwent additional thyroid surgery from three months to nine years later. At the end of the follow-up period, 9 patients had recurrent goiter (2 of these were malignant), 46 did not have goiter, and the status of 28 was unknown.

complete resection, received postoperative x-ray therapy. Radical neck dissection was not performed in any case. Of the nine patients with primary thyroid neoplasms who survived the postoperative period, four are living without recurrence 10 or more years after thyroidectomy, two have died of thyroid cancer, and three have died of other causes. Table 3 summarizes the data on the Category III patients with primary thyroid carcinoma.

TABLE 4.—*Present Status of Patients*

Classification	No. Patients	Alive	Dead	Lost	Surgery Later	Goiter			Tyroid Cancer
						Present	Absent	Unknown	
Category I (no surgery)	140	50	56	34	15	75	22	43	1*
Category II (adenomectomy)	80	43	14	23	4	7	55	18	2†
Category III (more Extensive surgery)	83	19	19	45	5	9	46	28	13

*Died of thyroid cancer.
†Apparently cured, living without recurrence at 21 and 22 years.

Thirteen patients of this group proved to have malignant goiter. One of these was metastatic; twelve had primary thyroid malignancies. The preoperative diagnosis was benign goiter in six cases, possible or probable cancer in six, and cancer in one. All of these patients had relatively conservative surgery—lobectomy, hemithyroidectomy, or bilateral subtotal thyroidectomy. One patient, who was thought to have had an in-

Tables 4 and 5 summarize the principal findings of this follow-up study.

Other Conservatively Treated Patients with Nodular Goiter

The Category I cases discussed above are a very small and selected minority of the nonoperated New Haven Hospital patients with nontoxic nodular goiter. Nodular goiter was not considered an important finding

TABLE 5.—*Evaluation of Clinical Selection: Frequency of Malignancy by Category*

Clinical Classification	No. Patients	Malignant at Time of Classification	Per Cent Malignant	Malignant Later	Patient-Years of Observation
Category I (no surgery)	140	1	0.7	0	1364
Category II (minimal surgery)	80	2	2.5	0	1136
Category III (more extensive surgery)	83	13	16	0	616

prior to 1945 unless hyperthyroidism were suspected. Examination of the thyroid gland, in most cases, was very casual, and many small goiters were overlooked. Many others were found on physical examination but were not coded as part of the official discharge diagnosis. The diagnostic index, therefore, yields only a small fraction of the total number of cases. A similar situation exists for many "minor" diagnoses, such as hallux valgus, nevus, epidermophytosis, etc. In general, the patients culled from the index were those whose goiters were symptomatic or of impressive size or those where there was some difference of opinion regarding management.

It is possible to estimate how many patients with nontoxic nodular goiter were examined at the New Haven Hospital between 1921 and 1945. Two surveys of the frequency of nodular goiter have been reported from New England. The autopsy study of Schlesinger and co-workers,[12] when corrected for age and sex distribution, suggests a frequency of 5% for the general population. The clinical study of Vander and co-workers [10] is especially significant because it is based on a large sample of presumably well adults. Three to four per cent of these people were found to have palpable nodular goiters. Age standardization might lower this slightly, to 2.5%-3.0%. The data of Vander and co-workers were accumulated between 1948 and 1953, when nodular goiter was somewhat less common than during the period represented by the data of Schlesinger and co-workers or the period covered by this study. A figure of 3% for the New Haven Hospital population of 1921-1945 is therefore a conservative estimate. Over 270,000 record numbers were assigned to patients during this period. Therefore, there must have been over 8000 patients with nodular goiter examined. The 140 patients listed in the diagnostic index are thus only a 2% sample of the total of "Category I" cases. Furthermore, they are not a representative sample. They contain a larger proportion of the possibly dangerous goiters.

On reviewing the charts of all patients diagnosed as having thyroid cancer prior to June 1955, five additional cases have been found in which nontoxic nodular goiters were described between 1921 and 1945 and in which thyroidectomy was not performed within six months. These patients were among the estimated 98% with nontoxic nodular goiter who are not listed under that diagnosis in the Record Room index.

CASE 4.—A 63-year-old white woman was first seen at the New Haven Hospital in 1935, following a fall in which she sustained a fractured skull, a subdural hematoma, and other injuries. A thyroid nodule 3×4 cm. was discovered on physical examination. It was not known how long this had been present. The patient was hospitalized for several months and made an essentially complete recovery. She was next seen in 1943, aged 71, complaining of goiter with pressure symptoms. She stated that her goiter had fluctuated in size from time to time but had gradually grown larger through the years. Six months prior to admission it began to grow rapidly, and soon became symptomatic. She had lost 16 lb. On examination, she was found to have a large firm mass in the right lobe of the thyroid, involving the isthmus and extending around the sternocleidomastoid. Preoperative diagnosis was "nontoxic adenoma, ? carcinoma." Right lobectomy was performed in March, 1943. The specimen weighed 81 gm. and contained cysts, degenerating adenomas, and fibrosis. No cancer was seen. Two months later, a rapidly growing recurrent tumor appeared in the right neck. The patient complained of hoarseness and difficulty in swallowing. A hard 6×4 cm. mass occupied the region of the right isthmus and the medial aspect of the left lobe. Biopsy revealed anaplastic carcinoma. Palliative surgery was performed. The patient died one month later of respiratory obstruction. Autopsy revealed extensive invasion of the neck organs and pulmonary metastases.

Comment.—It seems reasonable to conclude that this patient's goiter was benign in 1935, when it first was noted at the New Haven Hospital.

CASE 5.—This woman was found to have a uninodular goiter in 1922, when she was 69 years old. Operation was presumably not advised. The goiter increased in size gradually, reaching 8×5×5 cm. in 1928. Lobectomy was performed at this time because of the size of the mass and slight pressure symptoms. Preoperative diagnosis was "cystadenoma." Histological examination revealed papillary adenocarcinoma. In 1937, local recurrence of the carcinoma was found. The recurrent nodules

were excised in 1938. No additional therapy was given. The patient died in 1941, aged 88, of cardiovascular and renal disease.

Comment.—This patient probably had thyroid cancer in 1922 and should have had thyroidectomy at that time. However, her life expectancy was not affected by failure to operate.

CASE 6.—This Italian-born laborer gave a history of goiter since age 35. He was found to have a multinodular goiter in 1927, when he was 49. By 1938, the goiter had increased in size. Thyroidectomy was advised at that time but refused. He was next seen in 1940, with obvious thyroid carcinoma, cervical node metastases, and extension into the superior mediastinum. Lobectomy confirmed the diagnosis. He died in 1941, aged 64, of thyroid cancer.

Comment.—This patient probably did not have thyroid cancer in 1927, when his goiter was first described in the hospital record.

CASE 7.—This patient was born in Switzerland and had transient goiter in youth. In 1929, when she was 71 years old, she was found to have a 3×4 cm. nodule in the right lobe. She stated that it had been present for four years. It grew gradually. In 1930, it measured 6×7 cm. In 1940, the patient was admitted with a large, hard, irregular thyroid mass, pressure symptoms, and possible mediastinal metastases. She had hypertensive cardiovascular disease, smooth skin, fine hair, tachycardia, and lid lag. Basal metabolic rate was +20. Biopsy confirmed the diagnosis of thyroid cancer. The patient died in 1941, aged 82, of thyroid cancer.

Comment.—This patient probably did not have thyroid cancer in 1929, when her goiter was first described in the hospital record.

CASE 8.—This patient was hospitalized in 1942, when she was 51 years old, for cholecystectomy. She was found to have a multinodular goiter which she stated had been present at least five years. This increased in size and by 1947 was producing mild pressure symptoms. Lobectomy was then performed, with a preoperative diagnosis of "adenoma." Histological examination revealed papillary adenocarcinoma. A total thyroidectomy was performed after this diagnosis was established, and the patient has been maintained on dessicated thyroid since then. She was last seen in December, 1954, aged 63, and had no evidence of recurrence at that time.

Comment.—This patient probably had thyroid cancer in 1942 and should have had thyroidectomy at that time. Her life expectancy has so far not been affected by the failure to operate.

Adding these patients to those previously described, we arrive at a total of 8 thyroid cancers which have been diagnosed so far among an estimated 8000 patients whose nodular goiters were treated conservatively between 1921 and 1945. Five of these, or less than 0.1%, were probably malignant at the time of the original description. Three developed years later. Four of the eight patients died of thyroid cancer (including the three in whom cancer became manifest many years after the original diagnosis of nontoxic nodular goiter); one died of other causes, without cancer; three are alive without recurrence 7 to 22 years postoperatively.

It should be remembered, of course that the extent of follow-up of these estimated 8000 patients with nodular goiter is not known. An appreciable percentage have not been seen again at the Grace-New Haven Community Hospital. It is quite possible that some additional thyroid cancers have developed among these persons and have been treated elsewhere. It is very unlikely, however, that there were many such cases. The New Haven population is fairly stable, and patients who have been treated at the Grace-New Haven Community Hospital tend to return when they have a serious illness. Furthermore, thyroid cancer is seen somewhat more frequently at the Yale-New Haven Hospital Tumor Clinic than in the state of Connecticut as a whole [13]; this would not be the case if many of our patients were going elsewhere for treatment of thyroid cancer. Thus, the figures cited above may be a little too low but cannot be very far from the truth.

Comment

Ideally, classification of patients should be based on clinical estimation of the risk of malignancy, and, among the operated patients, on the reasons for surgery. In this study, however, this proved impossible. Such terms as "cancer suspected" and "cancer unsuspected" appear to be meaningless when assigned retrospectively. In most of these cases, the reasons for operating or not operating were not stated in sufficient de-

tail, and there was no uniformity in expressing the suspicion of malignancy. There were many cases in which small asymptomatic goiters were removed under the diagnosis of "nontoxic nodular goiter." Obviously, in many of these, fear of malignancy was a major reason for performing thyroidectomy, although it was not expressed in the preoperative notes.

The problem of classifying cases where operation was not performed is just as difficult. The records indicate that cancer was suspected in some patients not operated upon. One can only conclude that such recorded suspicion was smaller than the unrecorded suspicion among many of the operated cases. Contraindications to surgery and refusals by patients are also difficult to evaluate. Obviously, such complicating diseases as diabetes or arteriosclerosis would not bar surgery if there were strong likelihood that a goiter was malignant, although they might sway the decision if the probability of finding a cancer were considered small. Case 1 refused surgery. Had she been excluded from Group I for this reason, the incidence of malignancy would have been zero. However, it has been my experience that patients can usually be persuaded to accept surgery, if the doctor feels strongly enough that it is necessary.

A report from a group advocating thyroidectomy in all cases of nontoxic nodular goiter[3] presents an excellent example of this problem. Of 580 such goiters treated, only 261 were actually operated upon. There were many cancers in this group. Follow-up revealed no thyroid cancers among the other patients, where operation was "contraindicated" or "refused." It seems too much of a coincidence that all of the contraindications and refusals were in the benign group.

It was because of these problems that my admittedly harsh method of classification, using operation as the sole criterion of suspected malignancy, was adopted. This classification is simple, objective, reproducible, and generally applicable. It evaluates actual management of patients, rather than often vague clinical impressions.

It is obvious that clinical selection was the major factor affecting the observed incidence of malignancy in this series. Only one thyroid cancer has turned up among the 140 patients in Category I. (Ironically enough, this was in a patient who had undergone thyroidectomy 10 years previously.) Only a fraction of 1% of an estimated 8000 patients treated conservatively had cancer at the time of the original decision regarding therapy or have developed cancer since then. The findings in Category III are in striking contrast to the above. Sixteen per cent of the goiters selected for more extensive surgical treatment proved to be malignant. This is 20 times the frequency in Category I and 100 or more times the estimated frequency in the entire conservatively treated group. The efficiency of the preoperative selective process is impressive.

Some of the staff members responsible for the accurate selections reported here had had many years of experience with thyroid disease, others almost none. After many discussions of this problem with other physicians, I have concluded that the experience described in this paper is exceptional only in the unusually low number of thyroidectomies performed. Many others do just as well in selecting the dangerous goiters for surgery, but at most institutions a larger number of benign glands are operated upon. Where a conservative attitude toward thyroid surgery is the rule, as in this series, there will be a relatively high frequency of cancer among surgical specimens, even in the "cancer unsuspected" group. The reverse will be true in a series where most nodular goiters are extirpated, such as that of Watt and Foushee,[14] who found that only 1% of a relatively unselected group of nontoxic nodular goiters operated upon were malignant. There probably would have been more thyroidectomies at the New Haven Hospital, and a correspondingly lower incidence of malignancy among the surgical specimens, if several influential members of the staff had been less conservative in

their approach to the therapy of nodular goiter.

The follow-up period in this study totals about 3000 patient-years. No clinical evidence suggesting the appearance of a new thyroid cancer has been noted during this time. This observed low incidence of malignancy in a group of patients with nodular goiter confirms the estimates I have made previously,[6] as well as those of Crile and Dempsey[5] and of Miller.[8] Crile and Dempsey, Cerise and co-workers,[3] and Vander and co-workers[10] followed non-operated-on patients with nontoxic nodular goiter for shorter periods of time (less than 1000 patient-years of observation in each series) and also found no thyroid cancers. All authors who have studied this point thus agree that the incidence (new cases per unit of population per year) of malignancy among nontoxic nodular goiters is quite low.

Conservative management of nontoxic nodular goiter may be evaluated on two counts. It is obviously a failure in a patient who dies of thyroid cancer. It may also be considered a failure in a patient who subsequently undergoes thyroidectomy. By the first criterion, there is 1 known failure among the 140 patients in Category I and 4 among the estimated 8000 patients treated conservatively. By the second criterion, conservative management failed in about 10% of the patients in Category I. The deaths from thyroid cancer among the conservatively treated cases have been so few that they would almost certainly have been exceeded by operative deaths had all patients with nodular goiter been subjected to surgery. The 10% figure for subsequent operations in Category I is only a little higher than the corresponding percentage for Category III. Thus, the conservative management of selected cases of nontoxic nodular goiter appears to be thoroughly justified.

The study confirms the opinion of many experienced physicians that the great majority of nontoxic nodular goiters need not be extirpated. There are dangerous goiters, however. The criteria for selection of patients for surgery have been discussed by Rogers and co-workers,[9] Crile and Dempsey,[5] Cope and co-workers,[15] Sloan,[16] and many others. I agree with them that enlarging, firm, discrete tumors of the thyroid should be removed. Nodules producing distinct pressure symptoms are best treated surgically. On the other hand, soft, smooth, round nodules which do not grow may be left alone. Among older patients one may find somewhat irregular, partially calcified masses which have not changed in many years; these too may be ignored. Nodules appearing during pregnancy often regress spontaneously. Treatment with iodine or dessicated thyroid may produce regression of others. Clinical estimation of the number of nodules in a goiter is of little value. "Uninodular" goiters very frequently turn out to be multinodular; while the presence of two benign nodules confers no magical protection against the development of a third, malignant one.

A reasonable period of observation is justified in almost all cases. During this period it can be determined whether or not a nodule is enlarging. The effect of treatment with dessicated thyroid or iodine may be evaluated. The opinion of a more experienced consultant may be obtained. Since the prognosis in thyroid cancer depends principally on the biological characteristics of the tumor, and is little affected by minor delays in surgical treatment,[16-20] a physician may quite properly take several months to decide whether or not an apparently benign goiter should be removed.

Although, as has been demonstrated, preoperative selection in nontoxic nodular goiter is very accurate, it cannot be perfect. There will continue to be occasional deaths from thyroid cancer among conservatively treated patients. There will also continue to be occasional operative deaths among patients with benign goiter treated surgically. These exceptional instances should not form grounds for appeals to extirpate all goiters—or no goiters.

Summary and Conclusions

Long-term follow-up has been accomplished of 296 patients upon whom the diagnosis of nontoxic nodular goiter was made between 1921 and 1945. Only one of 140 patients selected for nonsurgical treatment proved to have thyroid cancer. It is estimated that there were 8000 patients in all who received no surgical therapy. Very few thyroid cancers have occurred among this group. In contrast, 16% of patients selected for thyroidectomy had cancer. These figures demonstrate impressively the efficiency of preoperative selection in nontoxic nodular goiter.

This study represents 3000 patient-years of observation of persons with nontoxic nodular goiter. No new thyroid cancers have become evident during this time. This confirms previous estimates that the incidence of malignancy in this condition is quite low.

It is concluded that conservative management of selected cases of nontoxic nodular goiter is justified.

Roswell Park Memorial Institute (3).

REFERENCES

1. Cole, W. H.; Slaughter, D. P., and Rossiter, L. J.: Potential Dangers of Nontoxic Nodular Goiter, J. A. M. A. 127:883-888, 1945.

2. Hinton, J. W., and Lord, J. W., Jr.: Is Surgery Indicated in All Cases of Nodular Goiter, Toxic and Nontoxic? J. A. M. A. 129:605-606, 1945.

3. Cerise, E. J.; Randall, S., and Ochsner, A.: Carcinoma of the Thyroid and Nontoxic Nodular Goiter, Surgery 31:552-561, 1952.

4. Majarakis, J. D.; Slaughter, D. P., and Cole, W. H.: Carcinoma of the Thyroid Gland, J. Clin. Endocrinol. 13:1530-1541, 1953.

5. Crile, G., Jr., and Dempsey, W. S.: Indications for Removal of Nontoxic Nodular Goiters, J. A. M. A. 139:1247-1251, 1949.

6. Sokal, J. E.: Incidence of Malignancy in Toxic and Nontoxic Nodular Goiter, J. A. M. A. 154:1321-1325, 1954.

7. Sokal, J. E.: Surgical Statistics on Malignant Goiter, Surg. Gynec. & Obst. 99:108-114, 1954.

8. Miller, J. M.: Carcinoma and Thyroid Nodules: The Problem in an Endemic Goiter Area, New England J. Med. 252:247-251, 1955.

9. Rogers, W. F., Jr.; Asper, S. P., Jr., and Williams, R. H.: Clinical Significance of Malignant Neoplasms of the Thyroid Gland, New England J. Med. 237:569-576, 1947.

10. Vander, J. B.; Gaston, E. A., and Dawber, T. R.: Significance of Solitary Nontoxic Thyroid Nodules: Preliminary Report, New England J. Med. 251:970-973, 1954.

11. Jaffe, R. H.: The Variation in Weight of the Thyroid Gland and the Frequency of Its Abnormal Enlargement in the Region of Chicago, Arch. Path. 10:887-894, 1930.

12. Schlesinger, M. J.; Gargill, S. L., and Saxe, I. H.: Studies in Nodular Goiter: I. Incidence of Thyroid Nodules in Routine Necropsies in a Nongoitrous Region, J. A. M. A. 110:1638-1641, 1938.

13. Sokal, J. E.: Occurrence of Thyroid Cancer, New England J. Med. 249:393-397, 1953.

14. Watt, C. H., and Foushee, J. C.: The Incidence of Carcinoma in Nodular Thyroids in Southwest Georgia, J. M. A. Georgia 40:414-417, 1951.

15. Cope, O.; Dobyns, B. M.; Hamlin, E., Jr., and Hopkirk, J.: What Thyroid Nodules Are to Be Feared? J. Clin. Endocrinol. 9:1012-1022, 1949.

16. Sloan, L. W.: Of the Origin, Characteristics and Behavior of Thyroid Cancer, J. Clin. Endocrinol. 14:1309-1335, 1954.

17. Frazell, E. L., and Foote, F. W., Jr.: The Natural History of Thyroid Cancer: Review of 301 Cases, J. Clin. Endocrinol. 9:1023-1030, 1949.

18. Crile, G., Jr.: Factors Influencing the Prevention and Cure of Cancer of the Thyroid, Surg. Gynec. & Obst. 91:210-214, 1950.

19. Harnett, W. L.: British Empire Cancer Campaign: A Survey of Cancer in London; Report of the Clinical Cancer Research Committee, London, British Empire Cancer Campaign, 1952.

20. Marchetta, F.: Carcinoma of the Thyroid, to be published.

An Intrafamilial Epidemic of Pharyngoconjunctival Fever

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Pharyngoconjunctival fever has become recently recognized as a specific viral disease entity characterized by fever, pharyngitis, and conjunctivitis occurring singly or in combination, in epidemic or sporadic form.[1-3] Virus-isolation studies and the subsequent development and application of APC group-specific complement-fixation and type-specific neutralization tests have shown that APC Type 3 virus is the etiologic agent.[1-4] Epidemics have been reported from widely separated areas.[2-5] Since this disease entity may be confused with a variety of other infections or may be mild enough not to require the services of a physician, many cases are probably not recognized or reported. It is the purpose of this study to describe the disease as it appeared in a family of seven.

Report of Cases

CASE 1.—A 12-year-old white boy was admitted to the Ohio State University Hospital on July 16, 1955, because of a six-day illness, characterized by pharyngitis, unilateral conjunctivitis, and fever, which had not responded to a variety of antibiotics. There was also mild diarrhea during the first two days of illness. Except for the usual childhood diseases his past medical history and system review were not remarkable.

Physical examination revealed a well-developed, well-nourished boy with a rectal temperature of 104 F, but not appearing acutely or chronically ill. The left conjunctiva showed marked follicular injection and edema, with some scleral injection and increased tearing. There was no purulent discharge or evidence of uveitis. Examination also revealed moderate serous nasal discharge, a granular injected pharynx, and enlarged cryptic tonsils, with patchy, yellow exudate in the crypts. There were many slightly enlarged nontender cervical and inguinal lymph nodes. The remainder of the physical examination was essentially normal.

Laboratory studies at this time showed a total white cell count of 4500, with 36% neutrophiles, 55% lymphocytes, and 9% monocytes. Routine urinalysis, chest x-ray, and spinal fluid examinations were all normal. Bacterial cultures from the nose, throat, conjunctivae, blood, and spinal fluid showed no pathogens. Serologic studies for typhoid, paratyphoid, and Brucella were negative, as were heterophile and cold agglutination tests. A tentative diagnosis of pharyngoconjunctival fever was made at this time. Virus isolation and serologic studies confirming the diagnosis are shown in the Table.

The hospital course was one of progressive improvement on purely symptomatic therapy and modified bed rest. He was afebrile two days after admission and was discharged on the fifth hospital day feeling well.

Since the family history revealed that six of the seven members had recently been or were presently ill, it was decided to study the entire family from the clinical and laboratory aspects.

CASE 2.—A one-year-old boy was the youngest sibling and the first member of the family to become ill, approximately eight days before Case 1. He had had no previous significant illnesses. On July 2, he developed abrupt onset of rhinitis and bilateral conjunctivitis. Although his temperatures were not recorded, his illness was characterized by six days of fever accompanied for the first two days by mild diarrhea and refusal of all feedings except fluids, which implied pharyngitis. When first seen by us, 15 days after the onset of his illness, physical examination revealed a healthy baby with no positive findings except multiple, nontender, slightly enlarged, cervical lymph nodes. His total white cell count at this time was 6750, with 16% neutrophiles and 84% lymphocytes. No virus was isolated from this patient, but serologic studies were consistent with the diagnosis of Type 3 virus infection (Table).

CASE 3.—A 14-year-old girl had been swimming on July 13 and had been exposed to a cousin with a "sore throat" from July 11 to 14. She

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From the Department of Medicine, Ohio State University College of Medicine and The Ohio State Health Department Laboratories.

Summary of Clinical and Laboratory Findings in APC, Type 3, Epidemic

Cases		1	3	4	2	7	6	5
Clinical Observations:								
Date of onset, July 1955		10	14	15	2	—	16	16
Fever		+	+	+	+	—	+	—
Pharyngitis		+	+	+	+	—	+	+
Conjunctivitis		+	+	+	+	—	—	—
Rhinitis		+	+	+	+	—	+	+
Malaise		+	+	+	+	—	+	+
Adenopathy		+	+	+	+	+	—	—
Cough		—	—	—	—	—	+	+
Diarrhea		+	—	—	+	—	—	—
Laboratory Results								
Virus isolation								
Eye		+	+	+	—	—	—	—
Pharynx		+	+	+	—	—	—	—
Stool		+	+	+	—	—	—	—
Blood		—	—	—	—	—	—	—
Serologic								
Neutralization Titer (APC-3)*	1	N.D.†	1:4	<1:4	1:4	1:4	<1:4	<1:4
	2	1:64	1:16	1:16	1:8	1:4	<1:4	1:4
	3	1:16	1:16	1:16	1:64	1:8	<1:4	<1:4
Complement fixation (APC-2)*	1	N.D.†	<1:8	1:8	1:8	1:8	<1:8	<1:8
	2	1:16	1:16	1:32	1:16	<1:8	<1:8	<1:8
	3	<1:8	<1:8	<1:8	<1:8	<1:8	<1:8	<1:8

*Sera 1, 2, and 3, taken at 1 wk., 6 wk., and 7 mo., respectively, after onset in all except Case 2, where intervals were 3 wk., 8 wk., and 7 mo. after onset.
†Specimen lost as result of laboratory accident.

also had been in daily contact with her siblings (Cases 1 and 2, above). On July 14, she noted the gradual onset of a "sore throat and runny nose," but no cough, chills, or fever. During the following two days she developed malaise, muscle aching, mild fever, and conjunctivitis. When seen by us five days later, July 19, she was afebrile, and her only remaining complaint was the persistence of pharyngeal symptoms. The positive physical findings included slight bilateral conjunctival injection and injected tonsils and pharynx. There was thick yellow-white exudate in the tonsillar crypts. Enlarged, nontender anterior cervical nodes were palpable.

Laboratory studies showed a total white count of 4150, with 40% neutrophiles, 59% lymphocytes, and 1% basophiles. The isolation of Type 3 virus confirmed the clinical diagnosis of pharyngoconjunctival fever (Table). Her subsequent clinical course showed rapid improvement, with complete disappearance of all signs and symptoms by the ninth day.

Case 4.—An 11-year-old boy became ill on July 15, which was 1, 5, and 13 days, after Cases 3, 1, and 2, respectively, when he awoke with rhinitis and red, swollen eyes. There was a slight amount of thin, conjunctival discharge and ocular pruritus, but no photophobia. Fever, with temperature up to 103 F (oral), developed the next day. He was first seen by us on the fifth day of his illness, at which time his temperature was 99.8 F (oral), pulse 90. He was a well-developed, well-nourished boy not appearing acutely or chronically ill. His right eye showed moderate peripheral scleral injection and an injected edematous, granular conjunctiva covered with a thin, clear discharge. There was only slight injection and edema of the left conjunctiva, and a clear nasal discharge. His tonsils were injected only mildly, but there was moderate pharyngeal injection and edema, with a patchy, white mucoid exudate in the post-tonsillar region. The remainder of the physical examination was negative, except for several enlarged, nontender anterior cervical lymph nodes.

Laboratory studies showed a total white cell count of 3925, with 40% neutrophiles, 53% lymphocytes, and 7% monocytes. Hospitalization was not thought to be necessary. His fever had completely subsided by the sixth day, and the conjunctivitis and pharyngitis cleared by the eighth day of his illness. Virus isolation and serologic studies confirmed Type 3 infection (Table).

Cases 5 and 6.—The parents, ages 37 and 35 years, respectively, developed pharyngitis and cough on July 16. Neither had conjunctivitis or rhinitis. Case 6 had a mild fever for one day; Case 5 had no fever. Their symptoms were much less severe than those of the children and lasted for only two to three days. Although both had suffered repeated upper respiratory infections in the past, they could not remember having had conjunctivitis, fever, and pharyngitis at the same time.

Physical examinations performed on July 19 were entirely negative.

Laboratory studies showed that Case 5 had a total white cell count of 17,200, with 70% neutrophiles and 30% lymphocytes. Case 6 had a total white cell count of 6250, with 46% neutrophiles, 52% lymphocytes, and 2% eosinophiles. As expected from the clinical course, virus studies for Type 3 infection were negative in both parents (Table).

Case 7.—A 2-year-old boy was not observed to be clinically ill during the period of illness

of the other members of the family or in the following six months. Past history revealed no symptoms suggestive of previous pharyngoconjunctival fever.

Physical examination on July 19 revealed mild generalized lymph node enlargement, but was otherwise completely normal.

Laboratory studies showed a total white cell count of 10,150, with 31% neutrophiles, 64% lymphocytes, 2% eosinophiles, and 3% monocytes. The negative virus studies supported the absence of clinical signs of disease (Table).

Materials and Methods

Virus Isolation Technique.—Swabs of each patient's conjunctivae and pharynx were placed immediately in separate sterile tubes containing 1 ml. of HeLa-cell maintenance fluid. Within 48 hours 0.1 ml. of the fluid from each specimen was inoculated into each of four HeLa-cell tissue-culture tubes.[6] Throat washings with 15 ml. of beef-heart-infusion broth were obtained from all members of the family, except the two youngest siblings, Cases 2 and 7. Each specimen was then centrifuged at 2000 rpm for 30 minutes and 1 ml. of the supernatant removed, to which 100 units of penicillin and 200γ of streptomycin were added; 0.1 ml. was then inoculated into each of three HeLa-cell culture tubes. Isolation from blood was attempted by inoculation of 0.1 ml. of macerated blood clot from each person into each of three HeLa-cell tubes. HeLa maintenance solution was not changed in any of the above specimens until the seventh day after inoculation, and the cells showed little evidence of nonspecific degeneration. Stool specimens were processed according to the technique of Scherer and co-workers,[6] and HeLa-cell maintenance fluid was changed the day after inoculation with stool extracts to reduce the effect of any toxic substances. All of the HeLa-cell tissue cultures were cultivated and maintained according to the technique described by Scherer and co-workers.[6]

Virus Serologic Studies.—Blood specimens were collected from each member of the family, as close to the acute phase of the illness as possible, and then approximately one and seven months later. The acute blood specimens were divided into two parts; one portion was inoculated into the HeLa-cell cultures for attempted virus isolation, and the other was held for serologic study. Complement-fixation tests, using Type 2 APC antigen, were performed on all sera; a modified Kolmer protocol was employed. HeLa-cell tissue culture neutralization tests using Type 3 APC virus were performed on all serum specimens. The virus used in the test was diluted to produce cytopathogenic changes on the second or third day.[7] Virus and serum controls were included with each test. A summary of the laboratory results is shown in the Table.

Comment

The clinical findings, consistent with pharyngoconjunctival fever, in three cases, 1, 3, and 4, were associated with successful Type 3 virus isolations and significant elevations of specific serologic titers (Table). These virus isolates were also typed at the National Institutes of Health in the laboratories of Dr. Robert Heubner, and the isolates obtained from these three members of this family were confirmed as Type 3 APC virus. No virus was recovered from Case 2, who was well at the time examined but had previously had the typical clinical history of pharyngoconjunctival fever. This is consistent with previous studies in which virus was isolated only during the active phase of disease.[3,4] No significant rise in titer was observed between specimens obtained from the patient, Case 2, during the third and eighth weeks of illness. However, the neutralization titer of a serum specimen obtained seven months after onset was positive at 1:64, as compared to previous 1:4 and 1:8 titers. Since there had been no intervening illness between these specimens, this patient (Case 2) could also be considered a proved case. Case 7, therefore, was the only child in the family who did not become ill during this period and showed correlative negative virus studies. The parents, designated as Cases 5 and 6, did not have the same type or severity of symptoms as the children. They failed to yield virus in HeLa-cell culture and showed no significant serologic titers. Their clinical signs, likewise, did not fit the pattern of pharyngoconjunctival fever. Thus, four of seven members of the family had infections with Type 3 virus. It is of interest to note that the clinical symptoms in these four children were strikingly similar in that all exhibited fever, conjunctivitis, pharyngitis, rhinitis, malaise, and cervical adenitis. Transient diarrhea was present in two of the four children. All responded to supportive ther-

apy alone. The incubation period was apparently between five to eight days as the disease progressed through the family.

Since a carrier state of this virus has not been previously demonstrated,[2-4] it is of interest to note that the virus was isolated in these studies only from the three acutely ill persons (Cases 1, 3, and 4) from the conjunctiva, pharynx, and stool. One month later, after they had recovered, no virus isolations could be accomplished.

As has been noted previously,[2-5] the complement-fixation titers, which are group-specific, and the type-specific neutralization titers both rose in all positive cases. Serologic studies were repeated on all members of the family at approximately seven months after the acute illness. Neutralizing antibodies at this time were present at a titer similar to that taken approximately one month after the onset of illness, except in Case 2, whose serum showed an eightfold increase in titer. Complement-fixing antibodies could not be demonstrated in any member of the family after seven months (Table). This observation suggests that the complement-fixation titer is transient in nature while the neutralization titer is more persistent. This dissociation of serologic tests has been suggested previously by Heubner and co-workers.[1]

Summary

The clinical and laboratory findings in an intrafamilial epidemic of pharyngoconjunctival fever are described. Results of this limited study are generally in accord with previous observations. APC virus, Type 3, was isolated from three of seven persons with acute illness. A significant rise in serologic titers occurred in four persons. Thus, four of seven members were proved to have pharyngoconjunctival fever. Although the group-specific complement-fixation test and the type-specific neutralization test rose equally during the acute phase of the illness, no complement-fixation antibodies were demonstrated seven months later, although the neutralization titers remained elevated.

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REFERENCES

1. Huebner, R. J.; Rowe, W. P.; Ward, T. G.; Parrott, R. H., and Bell, J. A.: Adenoidal-Pharyngeal-Conjunctival Agents: A Newly Recognized Group of Common Viruses of the Respiratory System, New England J. Med. 251:1077-1086, 1954.

2. Parrott, R. H.; Rowe, W. P.; Huebner, R. J.; Bernton, H. W., and McCullough, N. B.: Outbreak of Febrile Pharyngitis and Conjunctivitis Associated with Type 3 Adenoidal-Pharyngeal-Conjunctival Virus Infection, New England J. Med. 251: 1087-1090, 1954.

3. Bell, J. A.; Rowe, W. P.; Engler, J. I.; Parrott, R. H., and Huebner, R. J.: Pharyngoconjunctival Fever: Epidemiological Studies of a Recently Recognized Disease Entity, J. A. M. A. 157:1083-1092, 1955.

4. Ginsberg, H. S.; Gold, E.; Jordan, W. S., Jr.; Katz, S.; Badger, G. F., and Dingle, J. H.: Relation of the New Respiratory Agents to Acute Respiratory Diseases, Am. J. Public Health 45: 915-922, 1955.

5. Cockburn, T. A.: Epidemic of Conjunctivitis in Colorado Associated with Pharyngitis, Muscle Pain, and Pyrexia, Am. J. Ophth. 36:1534-1539, 1953.

6. Scherer, W. F.; Syverton, J. T., and Gey, G. O.: Studies on the Propagation in Vitro of Poliomyelitis Viruses: IV. Viral Multiplication in a Stable Strain of Human Malignant Epithelial Cells (Strain HeLa) Derived from an Epidermoid Carcinoma of the Cervix, J. Exper. Med. 97:695-710, 1953.

7. Rowe, W. P.; Huebner, R. J.; Hartley, J. W.; Ward, T. G., and Parrott, R. H.: Studies of the Adenoidal-Pharyngeal-Conjunctival (APC) Group of Viruses, Am. J. Hyg. 61:197-218, 1955.

A Clinical Evaluation of the C-Reactive Protein Test

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Introduction

In response to a variety of inflammatory lesions, there appears in the blood of humans a protein substance not normally present, which is identified by its capacity to form a precipitate with the somatic C-polysaccharide of the pneumococcus.[1] It has consequently been named C-reactive protein (CRP). Present knowledge points toward C-reactive protein being a β-globulin, probably bound to a lipid. Minute amounts of this protein may be demonstrated in human serum by a precipitin test employing a specific antiserum obtained from rabbits hyperimmunized by repeated injections of a purified C-reaction protein. In previous studies it has been demonstrated that the appearance of C-reactive protein in the blood is a nonspecific but extremely sensitive indicator of an inflammatory reaction due to infection. It has also been found in other disease processes of a noninfectious nature, such as malignancy and myocardial infarction. Kroop and Shackman[2] reported negative tests in six cases of coronary insufficiency without myocardial necrosis and positive tests in seven patients with myocardial infarction and coronary occlusion. CRP was detected as early as 36 hours after onset of symptoms and disappeared from the serum of one patient as soon as the 15th day of illness. In two cases, minute amounts of protein persisted during the fifth and sixth weeks of illness. Sprunt and Hale[3] reported positive tests in a large majority of patients with well-defined cancer. Negative tests occurred most frequently in early, but histologically proved skin cancers. They indicate that certain serological tests which have been proposed for cancer detection may be nonspecific and may be measuring C-reactive protein. Havens, Eichman, and Knowlton[4] reported on sera of 90 patients in various phases of viral hepatitis using the C-polysaccharide of pneumococcus in dilutions ranging from 1:5000 to 1:640,000. They considered this technique less sensitive and accurate than the C-reactive protein antiserum. No positive tests were obtained in any of the patients. The authors raised the question of whether a sufficient number of patients were tested in the earlier stages of the disease when inflammation is more active and might have caused positive tests. Shetlar, Bullock, Shetlar, and Payne,[5] in a study of 113 cases including normal persons as well as patients with a variety of diseases, revealed that C-reactive protein was present in a majority of instances of tuberculosis, Hodgkins disease, Ewing's sarcoma, multiple myeloma, and other malignant processes. These authors pointed out that the C-reactive protein is probably more closely correlated with seromucoid levels than with glycoprotein concentrations.

Elster and Wood[6] studied the C-reactive protein in the postcommissurotomy syndrome and pointed out the usefulness of this test in following cases pre- and postoperatively. They found that within 24 hours after surgery the test became positive and remained elevated as long as eight weeks. Seven patients under controlled studies following surgery for congenital heart disease had high test levels, but in only one case did it remain positive after one week. In 1950, Anderson and McCarty[7] demonstrated the usefulness of this test for the detection of rheumatic activity in patients

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with rheumatic fever. More recently, Ziegra and Kuttner [8] have observed the behavior of CRP in the serum of patients treated with antirheumatic agents. The C-reactive protein substance first discovered by Tillett and Frances, in 1930, is found in the acute phase sera of patients with pneumococcal pneumonia but gives no reactions in the convalescent phase. As pointed out above and by previous authors,[9] the CRP is not specific for pneumococcal pneumonia, but was found in the sera of patients with acute rheumatic fever, staphylococcal osteomyelitis, subacute bacterial endocarditis, Gram-negative bacterial endocarditis, and Gram-negative bacillary infections.

Material and Methods

The study was conducted as a routine laboratory procedure on a total of 729 patients admitted to various services of the U. S. Public Health Service Hospital, San Francisco. A total of 1262 tests was performed, using the capillary tube method employing C-reactive protein antiserum.* Repeat tests were performed when indicated and used as a guide to therapy and clinical progress of the various diseases studied. A column of antiserum about 2 cm. long and a column of the patient's serum of the same length were run into the capillary tubes. These were then set in a capillary tube rack, incubated at 37 degrees C for two hours, and then refrigerated for 22 hours. A 1 mm. column of precipitate was called a +1, and so on, up to 6 mm. for a +6 reaction. A +6 reaction was arbitrarily set as the maximum to be recorded.

Comment

Table 1 includes the group of infectious diseases known to be caused by Protozoa, fungi, bacteria, rickettsiae, and viruses. It consists of 163 cases of acute and chronic infectious processes tested during the various phases of infection. As can be seen from the Table, the number of patients

* C-reactive protein antiserum C-R-P-A, manufactured by Schieffelin & Company, New York.

TABLE 1.—*Infectious Diseases*

	Cases	Cases Initially Positive	Total Tests	Positive	Negative	Comment
Pneumococcal pneumonia	12	12	28	18	10	All cases initially positive and negative in convalescent phase
Acute pyelonephritis	6	5	10	5	5	Case initially negative not tested at onset of disease
Chronic pyelonephritis	5	0	5	0	5	All cases examined in quiescent phase and afebrile
Acute cholecystitis	2	2	5	2	3	Negative tests in convalescent phase
Chronic cholecystitis	10	2	18	2	16	Two cases with initial positive tests had jaundice and C-duct stone
Acute bronchitis	9	9	19	13	6	Negative in convalescent period
Acute tonsillitis	5	5	10	5	5	Negative in convalescent period
Chronic bronchitis	12	4	20	8	12	Three of cases with initially positive test had congestive heart failure
Bronchiectasis	6	4	10	5	5	Positive cases were febrile and moderately ill
Furunculosis and cellulitis	7	3	10	3	7	Moderate necrosis necessary for positive test
Tuberculous pericarditis	1	1	3	2	1	Tests negative after antitubercular therapy
Pulmonary tuberculosis, minimal and moderately advanced lesions	37	2	37	2	35	All hospitalized and on therapy at time of tests
Pulmonary tuberculosis, far advanced lesions	39	16	55	30	25	16 repeat tests in 3 months and 14 remained positive
Renal tuberculosis	1	1	2	1	1	Negative after therapy
Chancroid	2	2	4	2	2	Negative after therapy
Typhoid fever	1	0	3	0	3	Tested during second week of illness
Lepromatous leprosy	1	0	3	0	3	Advanced case of lepromatous leprosy
Spotted fever	1	0	1	0	1	
Coccidioidomycosis	1	1	3	2	1	Had osseous lesions; negative test after therapy
Amebic colitis	7	0	7	0	7	All negative
Suspected SBE	4	4	8	4	4	Negative in convalescent phase
Septicemia with bacteremia	1	1	5	3	2	Hemolytic Staphylococcus aureus organism
Meningococcemia	2	2	3	2	1	No follow-up in one case
Thrombophlebitis	13	13	22	13	9	All initially positive
Viral pericarditis	1	1	4	2	2	Negative in convalescent phase
Herpes zoster	5	0	5	0	5	All negative
Primary atypical pneumonia	7	2	14	4	10	Two of cases initially positive, one ill, with 1,600 WBC
Infectious mononucleosis	12	6	28	18	10	Positive in cases with moderate severity and exudative pharyngeal lesions
Mumps	3	0	3	0	3	
Lymphogranuloma inguinale	4	4	18	14	4	Tests remained positive for relative long period in disease
Common cold	10	3	14	6	8	
Latent syphilis	8	0	8	0	8	
Rubella	2	0	2	0	2	
Kaposi's varicelliform eruption	1	0	3	0	3	
Trichinosis	2	2	8	6	2	Negative after steroid therapy

initially showing a positive C-reactive protein total 107, or 65.6%. The majority were tested early in the period of their infections, with the exception of those having tuberculosis. The 107 patients out of the 163 tested is strong evidence, as reported in previous articles, that C-reactive protein is present in the acute phase sera of virtually all of the bacterial infectious diseases.

The more chronic disease processes, as tuberculosis, showed inconsistent findings, but correlated fairly well with the severity of the disease. As can be seen, of the 37 patients with minimal and moderately advanced lesions, only 2 tested positive. Of the 39 patients with far advanced lesions, 16 gave positive tests.

In the viral group of diseases, such as common colds, mumps, primary atypical pneumonia, herpes zoster, and infectious mononucleosis, the CRP test is less reliable. In the seven patients having primary atypical pneumonia, two cases gave positive tests. In the patients who had positive tests, the disease was severer than average. It was noted that in the infectious mononucleosis group the test was positive in the severe cases having vigorous febrile responses, high heterophile titers, and exudative and necrotic pharyngeal lesions.

The table shows a positive test during the acute phase in virtually all infectious bacterial diseases and a less consistent correlation in the chronic category as well as in the viral group. It was our observation that the C-reactive protein was not consistent with the erythrocyte sedimentation rate. The C-reactive protein was found to be a more sensitive test, being positive before the sedimentation rate fell and becoming negative in the convalescent phase before the sedimentation rate returned to normal.

Table 2 includes the group of gastrointestinal diseases, including metabolic disturbances. Of 213 cases tested, 47, or 22%, were initially positive. Certain gastrointestinal disorders complicated by infection gave positive reactions. Uncontrolled dia-

TABLE 2.—*Diseases of Gastrointestinal System Including Metabolic*

	Cases	Cases Initially Positive	Total Tests	Positive	Negative	Comment
Peptic ulcer	26	2	32	4	28	The 2 with positive tests were not explained
Peptic ulcer with hemorrhage	5	4	9	6	3	Negative after control of bleeding
Diabetes mellitus	19	1	20	2	18	Initial positive case was a severe brittle diabetic without infection, etc.
Diabetes mellitus with complications	6	6	18	14	4	2 cases of ketosis; 2 gangrene; 1 cellulitis, and 1 with ischiorectal abscess
Chronic hepatitis	18	0	18	0	18	Cirrhosis cases, some with hematemesis, ascites, etc.
Chronic hepatitis with toxic manifestations	5	5	10	5	5	All 5 cases had chills, fever, jaundice, leukocytosis, etc.
Fatty metamorphosis	2	0	2	0	2	Both cases palpable liver and positive biopsies
Recurrent cholangitis	2	2	4	4	0	2 cases of recurrent cholangitis
Intestinal parasites	10	0	10	0	10	Ascariasis, strongloidiasis, etc.
Hiatus hernia	5	0	5	0	5	2 had bleeding, but tests remained negative
Common duct stone with jaundice	3	2	6	4	2	2 cases operated and large common-duct stones found
Hepatoma with cirrhosis	3	3	6	6	6	All cases died within 2 months
Diverticulitis	3	3	6	3	3	Positive tests associated with fever; leukocytosis, elevated ESR, etc.
Acute pancreatitis	3	3	6	3	3	Negative in convalescent stage
Chronic pancreatitis	6	0	6	0	6	
Diverticulosis	6	0	6	0	6	X-ray diagnosis with no symptoms of active infection
Regional enteritis	1	0	3	0	3	Case tested in remission period of disease prior to surgery
Ulcerative colitis	3	2	8	6	2	Negative initial test was in remission
Alcoholism with gastrointestinal manifestations	13	4	30	6	24	Tests usually reverted to negative promptly
Acute gastroenteritis	8	2	10	2	8	Presumable viral in etiology
Acute infectious hepatitis	18	0	18	0	18	All tests negative in all phases of disease
Osteoarthritis	10	2	26	5	21	Two cases with positive tests were later diagnosed as osteo and rheumatoid types
Gout	6	6	14	9	5	All positive in relapse and negative in convalescent or remission stage
Hyperthyroidism	8	0	8	0	8	
Sheehan's disease	1	0	2	0	2	A 49-year-old woman with 15-year history of panhypopituitarism
Hypothyroidism	2	0	2	0	2	
Functional gastrointestinal tract disturbances	21	0	21	0	21	

betes mellitus with ketosis, cellulitis, gangrene, or infection also gave positive tests. As is seen in the Table, in diabetes mellitus without complications, only 1 case of 19 cases gave a positive reaction. This was a case of severe labile diabetes with no clinical or laboratory signs of accidosis, etc. The diseases of the pancreas and biliary system usually associated with infection gave positive tests. Acute infectious hepatitis was found to be negative in all tests performed. These findings confirm those of Havens and co-workers,[4] who reported negative tests in 90 patients tested in various phases of the disease.

In the metabolic diseases gout was found to test positively during the acute attacks with return to negative after medical treatment. In chronic hepatitis or cirrhosis the tests were negative except in the presence of toxic manifestations as exemplified by chills, fever, severe jaundice, emaciation, etc. Positive tests were obtained in all the three cases of hepatoma, two of which were diagnosed antemortem and one, postmortem.

Table 3 includes the diseases of the cardiovascular system in which the heart and entire vascular bed is considered as a unit. For the sake of orderliness, pulmonary infarctions and the postcommissurotomy syndrome are included in this group. One hundred twenty-seven cases were examined, and fifty cases were positive at time of the initial testing, representing 39%. Severe congestive heart failure showed a surprisingly high incidence of positive reaction, but was probably positive in a goodly number of instances on the basis of mild infection in the bronchial tree, as they all showed x-ray evidence of pulmonary congestion and some with fluid accumulations within the pleural spaces. Two cases of acute coronary insufficiency were initially positive, but also showed evidence of being in the "intermediate coronary syndrome."[10,11] They showed elevated sedimentation rates, mild febrile reaction, and a leukocytosis, but ECG changes were not definite enough to confirm frank myocardial infarction. Pulmonary infarctions were uniformly positive and continued positive in most cases for a relatively long interval, during the convalescent phase. Two cases had repeated pulmonary infarcts. One case was that of a 31-year-old physician who developed multiple pulmonary infarcts following a hernioplasty and was treated successfully with dramatic results by steroid therapy following his third infarct. The other case, showing repeated infarction, had ligation of the inferior vena cava following the fourth recurrence of infarction. Myocardial infarction was 100% positive at time of fresh infarction. The tests became positive in 24-48 hours and reverted to negative usually in 8-14 days in the cases that did not develop complications. One case of postcommissurotomy syndrome was studied and found to be strongly positive until after

TABLE 3.—*Diseases of the Cardiovascular System*

	Cases	Cases Initially Positive	Total Tests	Positive	Negative	Comment
Severe congestive heart failure	22	18	46	26	20	A high incidence in congestive failure
Mild congestive heart failure	6	2	8	2	4	
Angina pectoris	12	2	16	3	13	1 positive case—elderly man with CHF; 1 coronary insufficiency case
Essential hypertension	19	0	19	0	19	No malignant cases in this group
Pulmonary infarction	8	8	20	12	8	Negative in convalescent period
Buerger's disease	1	0	1	0	1	
Cerebral thrombosis	12	0	12	0	12	Negative regardless of severity
Hypertensive cardiovascular disease	10	0	10	0	10	No failure, angina etc., but enlargement, murmur etc.
Myocardial infarction	17	17	44	31	3	Positive 24-36 hr. after infraction
Rheumatic heart disease	12	0	12	0	12	No clinical sign of activity
Generalized arteriosclerosis	4	0	4	0	4	
Ventricular aneurysm	3	2	10	9	1	2 of 3 cases had intractable cardiac failure and died within 4 mo.
Postcommissurotomy syndrome	1	1	10	8	2	Tests remained positive 6 wk. following cardiotomy

three weeks of steroid therapy, when it reverted to negative following resolution of pleural and pericardial effusions. The three pathological conditions in this group for which the test showed consistently initial positive tests were myocardial infarction, pulmonary infarction, and severe congestive heart failure. Cerebral thromboses were usually negative, confirming the findings of Roantree and Rantz [12] that destructive processes strictly limited to conditions of the central nervous system did not result in the appearance of this protein substance in the sera.

Table 4 includes rheumatic fever, rheumatoid arthritis, periarteritis nodosa, lupus erythematosus, etc., commonly classified as the collagen group of diseases. The group of collagen diseases and other diseases commonly classified as diseases of sensitivity gave an impressively high incidence of positive tests. In this group 53 cases were examined, of which 34 gave initially positive reactions, representing 64%. As can be seen from the Table, all cases of acute rheumatic fever were positive, which coincides with reports and findings of other authors, principally of Stollerman and co-workers.[13] All cases of rheumatoid arthritis were positive initially except in the milder ambulatory cases, which also showed relatively low sedimentation rates. One case of periarteritis nodosa and one case of lupus erythematosus were studied over a period of several months, and both reverted to negative after steroid therapy. It was found, as previously reported by Ziegra and Kuttner,[8] that the C-reactive protein usually fell rapidly with steroid therapy. This test, in practically all instances, became negative before the erythrocyte sedimentation rate became normal. It is well known that abrupt withdrawal of corticotropin (ACTH) or cortisone early in the course of therapy may be and usually is followed by a prompt recurrence of rheumatic manifestations.[8,14] This so-called laboratory-rebound phenomenon was demonstrated in some cases in our series of rheumatoid arthritis. It was our observation that the disappearance of C-reactive protein from the sera during antirheumatic therapy with adrenocortical hormones or with salicylates is secondary to suppression of the inflammatory process rather than a primary effect of these agents upon the metabolism of the C-reactive protein. In our experiences even high doses of cortisone, prednisolone, etc., did not cause the CRP tests to become negative as long as rheumatic activity was in evidence clinically. An interesting observation was the high incidence of positive tests in penicillin-sensitivity reactions, in which the reactons were moderately severe, with rash, fever, and moderate edema.

TABLE 4.—*Collagen Diseases and Other Diseases of Sensitivity*

	Cases	Cases Initially Positive	Total Tests	Positive	Negative	Comment
Rheumatoid arthritis	16	10	50	27	23	Negative tests initially in mild cases
Rheumatic fever	6	6	18	12	6	All cases initially positive; negative after therapy
Periarteritis nodosa	1	1	7	4	3	Negative CRP after steroid therapy; relapse after stopping treatment
Lupus erythematosus	1	1	8	3	5	Negative after steroid therapy; relapse gave positive test
Penicillin reactions	8	6	16	6	10	Positive in severe cases with fever and joint symptoms
Loeffler's syndrome	2	0	4	0	4	Uneventful convalescence and negative tests
Bronchial asthma	7	2	13	5	8	Positive in 2 cases; 1 with bronchitis and 1 status asthmaticus
Acute glomerulonephritis	2	2	4	2	2	Recovery uneventful
Chronic glomerulonephritis	5	2	12	6	6	Tests positive late in disease with uremia, etc.
Nephrosis	2	2	7	7	0	Tests remained positive until death
Acute myositis	3	2	8	6	2	One case later diagnosed rheumatoid arthritis

The group in Table 5 consists of both benign and malignant lesions, primarily of the lung, prostate, rectum, and bowel. The group of neoplastic disorders shows 34 cases examined, of which 24 showed initial positive C-reactive protein reactions, representing 70%. The Table readily shows that

TABLE 5.—*Neoplastic Diseases (Benign and Malignant)*

	Cases	Cases Initially Positive	Total Tests	Positive	Negative	Comment
Small bowel neoplasm	2	0	2	0	2	Both benign at surgery
Small bowel neoplasm	2	2	2	2	0	Malignant lesions with widespread metastasis
Bronchiogenic carcinoma (early)	7	4	7	4	3	Some later positive in following groups
Bronchiogenic carcinoma with metastasis	8	8	18	12	6	2 lived over 14 months following a positive test
Bronchiogenic carcinoma with probable metastasis	4	2	8	4	4	
Bronchial adenoma	1	0	1	0	1	Alleviated by surgery
Postpneumonectomy	1	0	2	0	2	Pneumonectomy 1 year prior to test for carcinoma of lung
Carcinoma of rectum	2	2	4	4	0	1 inoperable; 1 had abdominoperoneal repair
Multiple myeloma	1	1	2	2	0	Patient had moderately advanced bone lesions
Carcinoma of prostate	4	4	6	6	0	All treated with surgery
Carcinoma of nasopharynx	1	1	8	8	0	Tested on several occasions
Carcinoma of tonsil	1	0	1	0	1	No adequate follow-up

benign lesions gave negative responses, while the malignant group gave a high incidence of positive reactions. Those with obvious metastases gave 100% positive tests, as previously reported by others. In our experience, a positive test for an undiagnosed lung lesion tended to support a diagnosis of bronchiogenic carcinoma rather than that of a tubercular lesion. As can be seen by referring to Table 1, bronchiogenic carcinoma gives a higher incidence of positive reactions than tuberculosis.

Table 6 includes diseases of the bone marrow and reticuloendothelial system and constitutes our smallest group. The lymphomas are included in this group rather than in the neoplastic group (as a matter of choice). Twelve cases are included in this group, of which only one case was initially positive. The only case of lymphoblastoma included was initially negative to CRP testing but became positive after mechlorethamine hydrochloride therapy and also after development of pleural effusion.

TABLE 6.—*Hematologic Diseases*

	Cases	Cases Initially Positive	Total Tests	Positive	Negative	Comment
Pernicious anemia	4	0	4	0	4	All cases tested in moderate hematologic relapse
Chronic myeloid leukemia	3	0	3	0	3	2 cases yet living and doing well
Idiopathic thrombocytopenic purpura	1	0	3	0	3	Not benefited by splenectomy
Familial hemolytic icterus	1	0	2	0	2	Tested during mild crisis prior to splenectomy
Lymphoblastoma	1	0	6	3	3	Positive after mechlorethaminehydrochloride and pleural effusion
Hodgkin's disease	1	1	8	8	0	Remains positive on steroid therapy
Polycythemia vera	1	0	1	0	1	Mild case of 4 years' duration

TABLE 7.—*Miscellaneous Diseases*

	Cases	Cases Initially Positive	Total Tests	Positive	Negative	Comment
Contact dermatitis	7	0	7	0	7	
Chronic brain syndrome	4	0	4	0	4	
Guillain-Barre syndrome	3	0	6	0	6	
Syncope	5	0	5	0	5	
Postconcussion syndrome	6	0	6	0	6	
Cointoxication	1	1	2	1	1	Negative test in follow-up
Hydronephrosis	3	0	3	0	3	
Psychoneurosis	5	1	5	1	4	Positive test
Epilepsy	10	0	10	0	10	
Conversion hysteria reactions	7	0	7	0	7	
Amyotrophic lateral sclerosis	2	0	2	0	2	
Hemorrhoids	6	0	6	0	6	
Fractures	2	0	2	0	2	Minor fractures in both cases
Postoperative testing	13	11	13	11	2	All had major operations
Essential albuminuria	6	0	6	0	6	
Observation (no diagnosis made)	32	0	32	0	32	
Fever of undetermined origin	3	3	10	5	5	Febrile illnesses of undetermined causes

The miscellaneous group in Table 7 comprises a varied group of pathological conditions tested during the experiment. It consisted of 127 cases, of which only 16 cases were positive. If the postoperative tests are excluded, the percentage of positives is 3.9% and consists of 5 cases. As can be seen from the Table, these five cases are as follows: one case of carbon monoxide poisoning which quickly reverted to negative after therapy; one case of psychoneurosis, and three cases of fever of undetermined origin. The test proved to be uniformly positive 24-48 hours following a major surgical procedure and usually was negative 7-8 days following the operation, provided no complications ensued.

Summary and Conclusions

Our experience with the C-reactive protein in 729 cases is reported. A total of 1262 tests was performed. Some comparisons are drawn between the results of the tests and the sedimentation rates.

The C-reactive protein has been reported to appear as an acute-phase response in a variety of abnormal conditions, such as trauma, infections, necrosis, neoplasms, and granuloma formations.[15] In this series it was consistently found in the sera of patients with bacterial infections, acute rheumatic fever, acute myocardial infarction, and widespread malignant processes. It was commonly, but not consistently, found in cases of rheumatoid arthritis, virus infections, and active tuberculosis.

The test was rarely found to be positive in limited primary carcinoma with no clinical evidence of metastases.

Any positive test is considered abnormal and should stimulate further investigative studies to determine the causative factor. The C-reactive protein proved to be a more accurate test than the sedimentation rate in the presence of inflammatory or necrotic processes. The test proved to be more sensitive than the erythrocyte sedimentation rate, often was positive before the ESR became elevated, and often became negative before the erythrocyte sedimentation rate returned to a normel level. In some diseases in which positive tests were obtained originally, the test was considered a useful guide as to the presence or absence of activity and correlated well with the clinical course in most instances. This observation may be useful in following patients while on steroid therapy.

The test is an extremely simple, useful procedure which readily lends itself to routine office or hospital practice.

Dr. Lowell A. Rantz, Professor of Medicine, Stanford University School of Medicine, gave suggestions and reviewed the manuscript.

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REFERENCES

1. Tillet, W. S., and Francis, T., Jr.: Serologic Reactions in Pneumonia with a Non-Protein Somatic Fraction of Pneumococcus, J. Exper. Med. 52:561 (Oct.) 1930.

2. Kroop, I. G., and Shackman, N. H.: Level of C-Reactive Protein as a Measure of Active Myocardial Infarction, Proc. Soc. Exper. Biol. & Med. 86:95 (May) 1954.

3. Sprunt, D. H., and Hale, W. M.: Proceedings of the American Association for Cancer Research, April, 1955, Vol. 2.

4. Havens, W. P., Jr.; Eichman, H. L., and Knowlton, M.: Failure to Find C-Reactive Protein in Viral Hepatitis, Proc. Soc. Exper. Biol. & Med. 75:108 (Oct.) 1950.

5. Shetlar, M. R.; Bullock, J. A.; Shetlar, C. L., and Payne, R. W.: Comparison of Serum C-Reactive Protein, Glucoprotein and Seromucoid in Cancer, Arthritis, Tuberculosis and Pregnancy, Proc. Soc. Exper. Biol. & Med. 88:107 (Jan.) 1955.

6. Elster, S. K., and Wood, H. F.: Studies of the C-Reactive Protein in the "Post-Commissurotomy" Syndrome, J. Clin. Invest. 33:931 (June) 1954.

7. Anderson, H. C., and McCarty, M.: Determination of C-Reactive Protein in the Blood as a Measure of the Activity of the Disease Process in Acute Rheumatic Fever, Am. J. Med. 8:445 (April) 1950.

8. Ziegra, S. R., and Kuttner, A. G.: Reappearance of Abnormal Laboratory Findings in Rheumatic Patients Following Withdrawal of ACTH or Cortisone (with Special Reference to C-Reactive Protein), Am. J. M. Sc. 222:516 (Nov.) 1951.

9. Ash, R.: Nonspecific Precipitins for Pneumococcic Fraction C in Acute Infections, J. Infect. Dis. 53:89 (July-Aug.) 1933.

10. Graybiel, A.: The Intermediate Coronary Syndrome, U. S. Armed Forces M. J. 6:1 (Jan.) 1955.

11. Freedburg, A. S.; Blumgart, H. L.; Zoll, P. M., and Schlesinger, M. J.: Coronary Failure: Clinical Syndrome of Cardiac Pain Intermediate Between Angina Pectoris and Acute Myocardial Infarction, J. A. M. A. 138:107 (Sept. 11) 1948.

12. Roantree, R., and Rantz, L. A.: Clinical Experience with the C-Reactive Protein Test, A. M. A. Arch. Int. Med. 96:674 (Nov.) 1955.

13. Stollerman, G. H.; Glick, S.; Patel, D. J.; Hirschfeld, I., and Rusoff, J. H.: Determination of C-Reactive Protein in Serum as a Guide to Treatment and Management of Rheumatic Fever, Am. J. Med. 15:645 (Nov.) 1953.

14. Bunim, J. J.; Kuttner, A. G.; Baldwin, J. S., and McEwen, C.: Cortisone and Corticotropin in Rheumatic Fever and Juvenile Rheumatoid Arthritis, J. A. M. A. 150:1273 (Nov. 29) 1952.

15. Abernethy, T. J., and Avery, O. T.: The Occurrence During Acute Infections of Protein Not Normally Present in the Blood: Distribution of Relative Protein in Patients' Sera and Effect of Calcium on Flocculation Reaction with C Polysaccharide of Pneumococcus, J. Exper. Med. 73:173 (Feb.) 1941.

Treatment in Internal Medicine

The Management of Acute Asthma

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It is important that each physician have clearly in mind measures to be undertaken when faced with the management of acute asthma. Prompt treatment for this medical emergency may indeed prove to be life-saving. When one is faced with a severe attack of acute asthma, one often has little opportunity to review measures to be undertaken. Also, there may be little opportunity to secure consultation of someone with a particular interest in the management of asthma.

This discussion is being limited to the treatment of asthma in the acutely ill patient. There are fewer differences of opinion here, whereas in the long-term management of asthma many divergent attitudes exist.

Objectives in Treatment

The main objective in the treatment of asthma is to achieve prompt and lasting relief from the paroxysm of respiratory distress. For first consideration then is the relief of acute bronchospasm. When bronchospasm has been relieved, one then may direct his attention toward measures which will promote healing in the underlying bronchitis. Bronchitis is present in varying degrees in all asthmatic patients. There are many facets to the problem of controlling bronchitis. First, one will achieve this objective by removing the patient from those noxious substances to which he may be allergic or which are irritating his bronchi in a nonspecific manner. Next, one wishes to obtain rest in every way possible for the inflamed respiratory mucous membranes. This can be achieved by reducing physical activities, preferably with rest in bed. One can reduce the irritation associated with excessive coughing. One can correct the element of dehydration which is usually present in acutely ill asthmatic patients and which favors the inspissation of bronchial secretion. Next, one may combat certain infections by use of appropriate antibiotic drugs if such are indicated. One must take into consideration other causative factors, diseases, and complications, such as chronic sinusitis, obstructive bronchial lesions, and emotional disturbances, which may be aggravating asthma.

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Symptomatic Relief

Bronchodilators.—Epinephrine: The most effective bronchodilator in the management of the acute attack of asthma is epinephrine by hypodermic injection. This is the first medication to be used when an attack warrants treatment of this degree. Epinephrine should be administered in adequate doses and sufficiently often. The inadequate or delayed use of epinephrine in the treatment of asthma is likely responsible for more harmful results than is its excessive use. In the patient who has the relative contraindications of old age, of vascular disease, or of moderate hypertension, greater stress may arise from the struggle with severe asthma than might occur from small amounts of epinephrine administered to relieve the asthma. The patient should be encouraged to take epinephrine early in the treatment of an asthmatic attack. Often an injection of epinephrine which will afford

relief when taken early is more effective than larger doses required when an attack of asthma is allowed to become advanced.

My colleagues and I usually administer by hypodermic injection 0.25 to 0.50 cc. of a 1:1000 aqueous solution of epinephrine hydrochloride. Such a dose may be repeated several times at 20-minute intervals when sustained severe asthma necessitates this frequent use of medication. We prefer the use of an aqueous epinephrine solution to one dissolved in oil or otherwise designed for retarded absorption. While it is true that such devices extend the period of an epinephrine effect, they may permit uncontrollable absorption of the drug at times when it is less urgently needed. If facilities for repeated injections are available, an aqueous solution is preferable.

Recent evidence suggests that in the so-called "epinephrine-fast" patient, a restoration of the epinephrine effect may be achieved through correction of acidosis, which may be present in severe asthma. This may be accomplished through the intravenous use of sodium lactate in selected instances.[1]

It is desirable for a patient who may need repeated injections of epinephrine to be instructed in the self-administration of this drug. If for this service he must be dependent on the early arrival of a physician, a relative, or a solicitous neighbor, he looks forward with greater anxiety to each attack of asthma. With such delays, more medication may then be needed to interrupt an attack which has become fully established.

The use of epinephrine may be conveniently achieved through nebulized solutions inhaled for the relief of mild asthma. Available preparations include a variety of concentrations of epinephrine usually ranging from 1% to 3%.

Isoproterenol: In recent years, successful attempts have been made to enhance, through modification of the molecule, the value of epinephrine used other than by injection in the management of asthma. Among these preparations my colleagues and I have usually preferred isoproterenol. An alteration to increase the molecular structure at the site normally occupied by a methyl group will, under certain circumstances, enhance the inhibitory action of epinephrine and will decrease its excitatory functions directly toward the cardiovascular system. On the basis of these studies, preparations including ethyl, isopropyl, or other groups have been developed for use in the management of asthma.[2,3] The most widely used variety of modified epinephrine is perhaps isoproterenol. This preparation is currently available in solutions of 0.25% to 1% in appropriate vehicles. Such nebulized solutions may be applied to the respiratory passages by hand-operated nebulizers or by the utilization of compressed oxygen or air. Such therapy provides prompt relief, yet relief which often is transitory.

The isopropyl derivative of epinephrine likewise may be administered as a powder.[4] Taken by insufflation, this form of the drug is available in cartridges containing 10% and 25% concentrations for use in an Aerohalor. The drug also is available in tablet form for use sublingually.[5] Here its effect is weaker and is helpful only in milder attacks of asthma. Isoproterenol should not be injected, since the cardiovascular effects may be excessive.

Ephedrine: An important bronchodilating drug is ephedrine. This induces an effect similar to, though somewhat less than, that of epinephrine. Ephedrine likely owes its effectiveness to its capacity to slow the rate of enzymatic destruction of endogenously produced epinephrine.[6] The therapeutic effect of ephedrine is sustained over four to six hours. The usual dose of ephedrine sulfate which my colleagues and I employ is 3/8 grain (24 mg.) administered orally at intervals of four hours. The preparations we use often contain a mild sedative to offset the untoward side effects induced by ephedrine.

Ephedrine-like Drugs: Certain patients may tolerate ephedrine poorly because of

untoward cerebral or cardiovascular symptoms, thereby limiting the drug's usefulness. Likewise, elderly men having urinary obstruction from prostate disease will not infrequently have that obstruction accentuated during the use of ephedrine.

In patients who tolerate ephedrine poorly, one may use bronchodilators such as methoxyphenamine (Orthoxine) hydrochloride or phenylpropanolamine (Propadrine) hydrochloride. The effect of these drugs on asthma is similar to that manifested by ephedrine. They are, however, often somewhat less effectual than is ephedrine in combating an attack of asthma.

Xanthine Derivatives: An important group of drugs in the management of asthma is that of the xanthine derivatives, of which aminophylline is the most important. Aminophylline is most effective when administered intravenously. In the management of severe asthma, this drug is administered in doses of 3¾ to 7½ grains (0.24 to 0.48 gm.). Usually this drug is administered by placing it in fluids which are being given intravenously. In the occasional critically ill patient, it may be necessary for the material to be injected directly into the vein, 3¾ grains being administered in the 10 cc. of diluent. If this drug is given directly into the vein, the administration should be very slow; untoward cardiovascular symptoms may develop with its rapid administration. Usually 3¾ grains of aminophylline are added to each liter of fluids given intravenously in the management of the seriously ill asthmatic patient.

Aminophylline dissolved in a small tapwater rectal instillation or given by rectal suppository is useful particularly for those patients who are awakened nightly by asthma. Seven and one-half grains of rectally administered aminophylline will often prevent an asthmatic attack in the night. The effect of such medication extends over an eight-hour period, making its bedtime use advantageous. Unfortunately, a perianal and rectal irritation develops in certain patients following the rectal use of aminophylline, thereby precluding its use by this route, or necessitating the use of allied preparations, such as theophylline-methylglucamine (Glucophylline).

Orally administered aminophylline is of some help; yet its potency is far weaker than that of aminophylline administered by the intravenous route. Many patients will find that, when receiving approximately 20 to 24 grains (1.3 to 1.56 gm.) daily, they will begin to be nauseated by the further administration of aminophylline. Certain persons in whom intolerances are greater will find nausea occurring after smaller doses. When the necessity for using aminophylline appears to be urgent, yet nausea interferes with its use, one may use the drug intravenously after sedating the patient with parenterally administered chlorpromazine.

Expectorants

The use of expectorants in the management of asthma is one aspect of treatment most commonly neglected. It is, however, perhaps the most important form of therapy directed toward bringing bronchitis under control. Expectorants alone are of much less benefit unless their use is associated with adequate hydration of the patient. This dependence on adequate hydration as a condition for the efficacy of an expectorant is another principle in the management of asthma which is often overlooked.

Iodides.—A most effective expectorant is an inorganic iodide salt. My colleagues and I most often use potassium iodide either as an aqueous solution or in an expectorant mixture containing approximately 5 grains (0.325 gm.) of potassium iodide in each fluidrachm (3.7 cc.). This is administered orally three or four times daily, freely diluted with water, after meals, and often also at bedtime. When gastric irritation is a problem, one may use enteric-coated tablets of potassium iodide to avoid abdominal symptoms associated with the use of the drug.

When the drug is well tolerated, the use of potassium iodide is indicated in all asth-

matic patients who are raising tenacious bronchial secretions. Its use is continued until bronchitis is improved. It is often the last medication discontinued. Unfortunately, many patients tolerate iodides poorly. In such patients an acne-like eruption, swelling of the salivary glands or other evidences of intolerance develop. When prescribing iodide preparations, one should also advise patients concerning the possibility of these intolerances. When minor acne occurs only after a prolonged use of iodides, one may use an iodide expectorant intermittently and in reduced doses, stopping short of the point at which an eruption occurs. If iodides are poorly tolerated, one must rely on other expectorants, such as ammonium chloride, although these are less effective.

Detergents.—In recent years, detergent solutions have been available for use by nebulization. The function of these nebulized solutions is to aid in raising inspissated bronchial secretions. Occasionally these preparations are helpful; however, many asthmatic patients find their use irritating. Such preparations are readily adaptable to use with "face tents" in adults and with open-top oxygen tents in pediatric practice.

Hydration

One of the most important aspects of the management of asthma concerns the matter of hydration. The acutely ill asthmatic patient has eaten poorly, has perspired freely, and usually has taken inadequate quantities of fluids to correct this excessive loss of fluid. This dehydration is one of the most frequently neglected problems in the management of asthma. This dehydration leads to further inspissation of bronchial secretions, which in turn tends to perpetuate the tiring cough.

One should encourage asthmatic patients to drink copious amounts of liquid, usually in amounts equal to a glass of water each hour they are awake. Among the first therapeutic measures for the asthmatic patient is the use of intravenous fluids. These serve to combat dehydration effectively. A freely running intravenous solution during that critical phase of the asthmatic patient's illness permits the use of substances more effective by this method of administration. It is good practice to permit 2 to 3 liters of fluids to be slowly injected over the first 24-hour period in which an asthmatic patient is brought under care. Thereafter, one can administer 2 liters of fluids daily, preferably in divided doses, one in the morning and one later in the day. The use of such fluids late in the day often permits a night with less asthma.

The fluid most commonly used is 5% dextrose in water. The dextrose serves to replace glycogen which has been decreased especially through numerous injections of epinephrine. Likewise, dextrose is important in nourishment of profoundly exhausted patients. One should usually avoid the use of quantities of sodium-containing fluids, particularly if steroid drugs are being used with an associated hazard of electrolyte disturbance.

The use of intravenous fluids is continued until a patient is improved and until adequate hydration has been accomplished, as evidenced by an increasing urinary output and thinning of bronchial secretions.

Aminophylline is usually added to each liter of intravenous fluids administered. Also the intravenous use of hydrocortisone early in the care of the asthmatic patient will be discussed. One other additive to intravenous fluids may occasionally be necessary, namely, sodium iodide. One may encounter a patient, usually postoperatively, who cannot take iodides orally and in whom inspissation of chest secretions dictates the early use of iodides to effect thinning of bronchial secretion. Under these circumstances an ampule containing 15 grains (0.975 gm.) of sodium iodide is added, once daily, to the intravenous solutions employed. No difficulty has been encountered in the use of both sodium iodide and aminophylline in a liter of 5% dextrose and water administered intravenously.

The enthusiastic hydration which I have described is applicable in the care of most

patients having severe asthma. There is, however, a certain group of patients in whom a question exists as to the possibility of congestive heart failure as a contributing element in the patient's respiratory distress. When the possibility of a limited cardiac reserve exists, it is wise to curtail the generous use of intravenous fluids until it is apparent that cardiac reserve is adequate to handle this quantity of liquid effectively. Until the adequacy of a patient's cardiac reserve is established, one should administer intravenous fluids far more slowly, usually limiting their use to 1 liter daily.

Sedatives

Patients who have asthma are often profoundly exhausted through loss of sleep and their struggle with dyspnea. They harbor mounting anxiety with failure to obtain relief from their repeated paroxysms. The judicious use of sedatives may help in achieving the rest that such patients urgently need. There are principles to be kept in mind, however, in sedating the asthmatic patient. Of paramount importance is the avoidance of those drugs that depress the respiratory center. All opiate drugs are in this category. Likewise, in the use of sedatives, it is well to avoid those that depress the cough center. One wishes to leave the cough reflex intact as a precaution against the development of atelectasis. It is important to avoid excessive sedation of the asthmatic patient. Preparations employed in the management of asthma often contain small amounts of barbiturate drugs to combat their side-effects. The summation of these sedatives may total an excessive amount of medication. It should be noted that asthmatic patients often respond atypically to sedatives and, indeed, may be stimulated by such drugs.

Among the medications used for sedation, perhaps the barbiturate group of drugs has proved most helpful, assuming that a patient tolerates their use. Chloral hydrate seems to be well tolerated by most asthmatic patients and is unlikely, in ordinary doses, to suppress the respiratory center. Ataractic drugs are proving most helpful in sedating the asthmatic patient with little depression of the respiratory center. We have used chlorpromazine and meprobamate most effectively in controlling the element of tension manifested by many asthmatic patients.

Antihistamine drugs play a relatively unimportant role in the management of patients considered in this review. When asthma stems mainly from extrinsic factors there may be some therapeutic help from antihistamine drugs. The sedative effect afforded by several antihistamine drugs is at times a useful adjunct. They may be used orally or intravenously.

Cortisone-like Drugs and Corticotropin

With the introduction of steroid drugs, a powerful weapon in the control of asthma has been acquired. The use of these drugs, however, is but one facet in the management of asthma. Their use in proper amounts is usually followed by prompt control of asthma. It should be pointed out, however, that soon after the drugs have been discontinued, the asthmatic patient is again having difficulty, which is most often no worse and no greater than that present at the time steroid therapy was started. Patients deriving sustained benefit following the use of steroid drugs are the ones who have been able to correct adequately, during their brief respite from asthma, those factors responsible for, or contributing to, the problem of asthma. Unless other therapeutic objectives are achieved, approximately half of asthmatic patients are having trouble within a week of the time the steroid drug is discontinued. The average duration of benefit is approximately three weeks after the time the drug is stopped.

The problems associated with continued use of these drugs make it important that they not be started without compelling indications. One may encounter considerable difficulty in discontinuing steroid drugs after their prolonged use. Asthmatic patients who can achieve relief by measures

other than the use of these drugs certainly should do so.

Plan of Treatment.—My colleagues and I prefer to use steroid drugs, if they are indicated, in brief intermittent courses, rather than with a continuous program of therapy. The courses which we have employed usually have extended from a few days to three weeks, regardless of which of the drugs may be employed. We prefer to avoid the continuous use of these hormones because of their known capacity to suppress the adrenocortical function. Unfortunately, asthma is a disease wherein periodic severe stress is encountered. It is apparent that any procedure likely to suppress the capacity of the body to handle severe stress should especially be avoided in asthmatic patients. In addition to this contraindication, one has the other classic contraindications to the use of steroid drugs, including their effect on such problems as diabetes mellitus, duodenal ulcer, tuberculosis, pyogenic infections, and emotional instability.

Indications for Use.—There are definite indications for considering the use of the steroid drugs. A first indication in a seriously ill patient concerns asthma which, after a reasonable trial of more conservative measures, is failing to subside. At times one must without delay treat by steroid drugs a critically ill patient in whom there would appear to be disastrous consequences from deferring their use. Increasingly, there is an indication for the use of steroid drugs for the asthmatic patient who has severe symptoms and who has used large quantities of steroid drugs in the past. Here the concern is in permitting potentially frail persons with suppressed adrenocortical function to struggle in the throes of severe asthma. In certain patients, there may be urgency in controlling asthma, as illustrated by the preoperative patient suspected of having a malignant lesion and for whom surgical care had best not be long deferred. Another preoperative indication concerns the patient in whom control of cough is most urgent, as with the anticipated repair of a ventral hernia.

Precautions During Use.—During the administration of steroid drugs, there are certain precautions to be carried out. One should make frequent observations of the blood pressure and of urinalysis and should weigh patients daily. Aberrations in salt and water metabolism are usually reflected in rapid gains of weight. Patients should be observed for unusual cerebral stimulation, often indicated early by unusual wakefulness. Any new symptoms or change in the course of the patient's illness should be reviewed in the light of a possible metabolic disturbance owing to the use of steroid drugs. With the use of cortisone, especially if prolonged, one must consider the use of potassium supplements and restrictions concerning the use of sodium. With prednisone and prednisolone, however, the use of such supplements and restrictions is less frequently required.

Drugs Used.—Cortisone: Next, in reviewing the use of specific steroid drugs, I should like to consider cortisone. When this drug is employed, it is usually given orally with a dose of 300 mg. the first day to induce an early effect. It is then given in a reduced dose of 200 mg. daily thereafter. With the advent of definite symptomatic improvement, the dose is continued at 100 mg. daily over several days until near the end of the course of therapy. It is then tapered over a few days and stopped. Each daily dose is divided into three or four equal parts and administered at intervals of six to eight hours. Most courses which we administer are no longer than three weeks in length. The rate at which the drug in the final days of its use is tapered varies somewhat, depending on the length of time it or other steroid drugs have been administered. Usually the drug is tapered at approximately the rate of 12.5 mg. each two days.

One can best rely on cortisone injected intramuscularly for those patients who are to have operative procedures done. Such

patients are prepared preoperatively with 200 mg. of cortisone intramuscularly 48 hours before, 24 hours before, and on the day of operation. The use of the medication is continued postoperatively until the patient is beyond significant stress associated with the surgical procedure or until oral medication can supplant that which is injected. In calculating a patient's needs with respect to injected cortisone, it is well to keep in mind that an injected amount is absorbed and is effective over perhaps a period of two to three days, whereas the effect of the orally administered medication has largely been dissipated within six to eight hours. For this reason, though the injected dosage might be discontinued on the day of operation, there will nevertheless be a continuing steroid effect for at least an additional two days. An advantage in the use of cortisone consists in its now more reasonable cost. It does, however, present problems with disturbance of salt and water metabolism more readily than will prednisone and prednisolone, which will be considered later.

Hydrocortisone: Hydrocortisone is of special use in the management of asthma because of its greater solubility in water than cortisone, making its application to varying needs more widespread. Generally, the use of hydrocortisone is essentially interchangeable with that of cortisone. However, somewhat smaller doses, perhaps 75% to 80% of those employed with cortisone, will be effectual in the management of a patient by hydrocortisone.

The principal use for hydrocortisone in the management of asthma concerns rapid induction of a steroid effect. When an early effect is urgent, one may dissolve 100 mg. of hydrocortisone in the first liter of 5% dextrose in water administered intravenously. For a critically ill asthmatic patient with suppressed adrenocortical function from previous steroid therapy, hydrocortisone administered intravenously will provide effective supportive treatment, as well as help in the management of his asthma.

Prednisone and Prednisolone: Both prednisone and prednisolone have proved to be most useful in the management of the seriously ill asthmatic patient. These hormones are considered together because they are essentially interchangeable with respect to therapeutic results and effective dosage.

Generally, patients tolerate prednisone and prednisolone with less disturbance to their salt and water metabolism than that which is encountered with the use of cortisone and hydrocortisone. Prednisone and prednisolone, when administered in adequate doses, will promptly and effectively bring most asthma under good control. It is good practice to administer these drugs every 6 hours, particularly during the more troublesome phase of the acute asthmatic attack, using 10 mg. at 6-hour intervals for the first 24-hour period. The dosage may then be decreased over the succeeding two or three days until a dosage of 5 mg. each six hours is being administered. This dosage is maintained until near the end of a course of therapy, when it is tapered at the rate of perhaps 2.5 mg. each two days. Patients who are dependent on the use of prednisone or prednisolone in the management of their asthma often begin to have symptoms when the maintenance dose of prednisone or prednisolone is reduced beneath a range which varies from 12.5 to 17.5 mg. in daily divided doses.

Corticotropin: With respect to corticotropin, there has been a variety of useful programs of therapy available. Initially, this drug was used at intervals of every six hours and was used intramuscularly. Soon thereafter this use of the hormone was supplanted by its administration in smaller dosage, such as 20 mg., administered over an eight-hour period in intravenous fluids, usually once daily. The inconvenience of such a prolonged intravenous injection was largely overcome by placing corticotropin in a gel form for prolonged absorption. With this gel we have usually administered 20 units intramuscularly at 12-hour intervals, with a total daily dose of 40 units. With improvement this total daily dose is halved.

There are limitations to the use of corticotropin, one of the more significant ones growing in importance with passing time. If corticotropin is to prove effectual, the patient must have an adequately functioning adrenal cortex. Asthmatic patients who now present themselves for care have often received steroid medication in sizeable doses and for long periods. With such patients one must be certain that corticotropin is actually inducing the desired therapeutic effect. If indeed a patient is seriously ill, it may be more desirable to give the steroid therapy directly than to rely on corticotropin to stimulate the body to release steroid hormones from its adrenal cortex.

Another limitation concerns the necessity for injecting corticotropin. While this poses no great problem in the hospital, nevertheless, for the convalescent asthmatic patient who is dismissed from the hospital the constant need for such injections may continue to pose a problem.

Corticotropin has been used by some with the hope that by its use there may be less ultimate hypofunction in the adrenal cortex than might otherwise develop. Unfortunately, we have failed to see a significant sparing of adrenocortical function in those patients who have continuously received corticotropin along with or intermittently with steroid drugs.

The greatest use for corticotropin in the management of asthma remains with that group of patients in whom the matter of an injection is of little moment, in whom there has been a less extensive use of steroids, and in whom the urgent necessity for an early therapeutic effect from steroids does not exist.

Gas-Inhalation Therapy

Under certain circumstances the use of therapeutic gases represents an important adjunct in the management of severe asthma. The most pressing therapeutic indication for the use of oxygen is cyanosis in the asthmatic patient. One may also consider the use of such therapy in a profoundly exhausted patient, when associated inflammatory diseases exist, or with associated congestive heart failure.

The method by which gases are administered varies in accordance with the patient's needs. For most patients having intermittent acute attacks of asthma my colleagues and I find the use of the BLB mask most desirable. It lends itself readily to the intermittent needs of the asthmatic patient. The mask may be applied or removed according to these needs. When a patient is constantly in need of oxygen, the tent or the nasal catheter, preferably the former, may be used.

With the administration of oxygen, gas is allowed to flow at a rate of 6 to 9 liters per minute. When using the BLB mask the rate of flow is adjusted so that at the height of inspiration there still remains a small amount of gas in the rebreathing bag.

Occasionally my colleagues and I have used a mixture of 80% helium with 20% oxygen in treating asthma. This mixture may be used directly or further diluted with an equal part of oxygen from a second tank. While we have had the clinical impression that a mixture of helium and oxygen is somewhat more effective than oxygen alone in the management of severe asthma, this point has not been borne out by experimental studies.[7] One should caution the patient about a change in the quality of the voice while a helium and oxygen mixture is being inhaled. The voice assumes a high-pitched squeaking character which may induce concern.

The use of oxygen therapy in patients having advanced pulmonary emphysema may occasionally be associated with loss of consciousness. In such persons oxygen want has afforded a critical stimulus to the flagging respiratory center. A sudden cessation of this stimulus following oxygen therapy may result in a depression of the respiratory center, apnea, and unconsciousness. In such patients if oxygen is to be used it must be used in sharply curtailed quantities which will afford a measure of relief but which will not remove the critical

stimulus that oxygen want affords the respiratory center.

Another gas that is most useful in the management of asthmatic patients is carbon dioxide, especially in postoperative patients. Here bronchial secretions may collect in the lung bases with the resulting threat of atelectasis. Such a circumstance may occur following surgical procedures in the upper part of the abdomen. To breathe deeply is most uncomfortable; hence, these patients tend to splint the diaphragm. A few inhalations of 95% oxygen and 5% carbon dioxide given at hourly intervals will bring about deep respiration, thereby adequately ventilating the lung bases. This is an effective measure in reducing the incidence of postoperative atelectasis in asthmatic patients.

Most commonly, therapeutic gases may be administered at prevailing barometric pressure. There are, however, certain devices, such as the "Bennett valve" and "mine safety valve," which permit the asthmatic patient to breathe gases at somewhat greater than barometric pressure. With pulmonary edema the use of therapeutic gases under increased positive pressure may indeed prove lifesaving. In patients in whom no element of pulmonary edema exists we have encountered only an occasional patient who prefers the periodic use of positive-pressure breathing devices. It is of interest that asthmatic patients commonly exhale against partially closed lips, thereby inducing a degree of positive-pressure respiration.

Hospitalization

In the management of asthmatic patients it is desirable to place the patient in a hospital. This measure removes the patient from various substances to which he may have grown allergic within his home environment. It immediately removes him from dust, feathers, animal danders, and other offending substances which may aggravate his asthma. Many hospital rooms are provided with filtered air to prevent contact of the patient with pollen to which he may be sensitive. In the home great anxiety is induced in the relatives of the asthmatic patient when, in spite of therapeutic measures being undertaken, he is failing to respond well to such treatment. The mounting anxiety among solicitous relatives does not go unnoticed by the anxious patient. Another helpful aspect of hospitalization is the rest which it provides. Patients having asthma invariably have an element of bronchitis which is beneficially affected by rest.

It is desirable for the asthmatic patient to be placed in a private room if one is available. Asthmatic patients have their greatest difficulty during the night hours, thereby disturbing the rest of other patients. Visitors in wards may serve to bring dust, cosmetics, fur coats, and other potentially offending substances into the presence of the asthmatic patient. This problem is best solved by initially placing the patient in a private room. Likewise, it proves difficult to control feathers and dust from other beds without serious interference with nursing procedures. Other patients' use of tobacco and preference for open windows may serve to embarrass the asthmatic patient as he attempts to control his environment.

Hospitalization allows urgently needed medications to be administered promptly. Many medications must be given parenterally, and this is often more readily accomplished in the hospital than in the home. An added benefit from hospitalization concerns compassion for the exhausted relatives who have been charged with managing the seriously ill asthmatic patient. Usually the routine hospital fare is adequate in the management of the acutely ill asthmatic patient. When a history of intolerance to foods exists, appropriate modifications in this diet can be made pending an opportunity for a more complete allergy investigation.

Objectionable Practices

There are several practices used at times in the management of asthma which are objectionable. Paramount among these is

the use of medications which suppress the respiratory center. At no time should opiate drugs be given to the asthmatic patient. Those patients who die from asthma often do so following administration of such drugs. Likewise, opiate drugs have an untoward effect in suppressing the cough center, which is closely associated with the respiratory center. One should avoid the use of codeine-containing cough medications because of this desirability of keeping the cough reflex intact. Undue suppression of the cough reflex may lead to atelectasis.

Noxious fumes from burning stramonium either as a powder or as cigarets should be avoided. It is true that the smoke of burning stramonium will often relieve attacks of asthma. The disadvantages offset this advantage, however, because of marked irritation that such smoke induces in the respiratory mucosa. The frequent use of such powders is associated with a progressively severe chronic bronchitis.

Among objectionable practices one should include smoking. Many times the inveterate smoker protests that only through inhaling tobacco smoke is he able to release secretions in his bronchi. He employs smoke as a counterirritant, its usefulness resulting from the coughing paroxysm which it induces. I have found that one must unequivocally insist that asthmatic patients discontinue smoking. Any transitory benefit associated with the use of tobacco smoke is vastly offset by the major aggravation of the chronic bronchitis resulting from smoking.

At this point, it might be desirable to consider the "habit overcough" which many patients have, and the fact that many patients have actually been encouraged by physicians to cough hard in order to raise sputum. Unfortunately, the element of habit overcough is often one of the important factors perpetuating bronchitis in the asthmatic patient. After hydration has been effected and when bronchial secretions have been thinned it is well to encourage patients to suppress their tendency to cough hard. Through the rest to the bronchial mucosa afforded by the elimination of unnecessary irritative coughing the bronchial mucosa can readily undergo reparative process. Surprisingly many asthmatic patients look on all sputum as noxious stuff which must be raised continually to avoid serious difficulties within the chest. One should discuss the significance of this mucus with patients and attempt to reverse their belief in the necessity for hard coughing to produce sputum.

Another objectionable practice concerns the use of arsenic preparations. While it is true that certain patients derive benefit from the use of arsenical drugs in the management of their asthma, generally the use of these drugs should be discouraged. The early and late manifestations of heavy-metal intoxication make the use of arsenic hazardous.

One other objectionable practice concerns the early counsel which many asthmatic patients receive to seek another climate. With such admonitions there is an implied counsel that asthma will favorably respond to seeking a warm, dry climate. Unfortunately, this is often not the case.

Management of Bronchitis

An important objective in the management of the asthmatic patient is to bring about conditions favorable to the control of bronchitis. Each patient who has asthma has a greater or less degree of bronchitis. Many measures already considered in detail are specifically directed toward its treatment. Other measures also may be helpful, especially when bacterial infection is present.

An important element of bacterial infection in bronchitis may be suggested by fever, by the purulent nature of the sputum, or by evidences in thoracic roentgenograms of complicating inflammatory change. When bacterial infection exists, sputum should be studied to determine the prevailing organisms present. If the control of infection poses a significant problem, bacterial antibiotic-sensitivity studies should be under-

taken to determine which drugs are more exactly suitable. Often therapy must of necessity be started prior to the time when this information is available; yet treatment may be modified as antibiotic-sensitivity studies are completed.

In patients in whom prolonged antibiotic treatment is necessary, one should repeat sensitivity studies periodically. One often observes a change in the flora of prevailing organisms. Those organisms affected by an antibiotic will disappear; yet, in their place there will be a growth of organisms whose resistance is great to the antibiotic drug being used.

In patients in whom a chronic purulent bronchitis responds slowly to therapeutic measures, one may use a nebulized antibiotic drug. A most useful one is penicillin. Here 200,000 units is dissolved in physiologic salt solution with a concentration of 20,000 units per cubic centimeter and administered by nebulization throughout the course of each 24 hours.

Without demonstrated evidence of significant bacterial infection, one should not employ antibiotic drugs in this group of allergic patients.

Further Studies

With the improvement of the asthmatic patient one is then able to investigate more widely those causative factors which have been important in bringing about the patient's illness. With the subsidence of the acute asthma one may proceed with a bronchoscopic examination if indications for this study exist. Intranasal surgical procedures to eradicate chronic sinus infection may be undertaken. At this time pulmonary-function tests may be undertaken to delineate more clearly a patient's pulmonary reserve as an aid in guidance in outlining therapeutic measures. Now emotional problems which are commonly encountered in asthmatic patients may be more specifically considered, and, if indicated, psychiatric help may be secured. At this time an allergy survey may be undertaken to determine more exactly the role of various allergens in the patient's illness. Heretofore these have been difficult to study because many medications introduced in the management of asthma may interfere with the skin reactivity.

Conclusions

In conclusion it should be stressed that the seriously ill asthmatic patient has a medical problem which frequently involves many systems. It is unusual for a patient to have asthma alone. The use of potent weapons in the management of asthma presupposes an accurate appraisal of the entire patient, not merely his respiratory symptoms, and especially not merely the immunologic aspect of his respiratory problem. Only if the entire patient, his other diseases, his emotional problems, and the ultimate effects of therapy being given him are reviewed can the best care for asthma be afforded.

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REFERENCES

1. Blumenthal, J. S.: Personal communication to Dr. L. E. Prickman.

2. Bubert, H. M., and Doenges, J. P.: "Ethyl-Nor-Epinephrine," a New Drug for Symptomatic Relief of Bronchial Asthma, Bull. School Med. Univ. Maryland 31:12-20 (July) 1946.

3. Gay, L. N., and Long, J. W.: Clinical Evaluation of Isopropyl-Epinephrine in Management of Bronchial Asthma, J. A. M. A. 139:452-457 (Feb. 12) 1949.

4. Krasno, L. R.; Grossman, M., and Ivy, A. C.: The Inhalation of Norisodrine Sulfate Dust, Science 108:476-478 (Oct. 29) 1948.

5. Baker, A. G.: Sublingual Treatment of Bronchial Asthma with a Potentiated Isopropyl Arterenol Preparation, Ann. Allergy 11:49-52 (Jan.-Feb.) 1953.

6. Wright, S.; Maizels, M., and Jepson, J. B.: Applied Physiology, Ed. 9, New York, Oxford University Press, 1952, p. 510.

7. Schiller, I. W.; Lowell, F. C.; Lynch, Mary T., and Franklin, W.: The Effect of Helium-Oxygen Mixtures on Pulmonary Function in Asthmatic Patients, J. Allergy 26:11-15 (Jan.) 1955.

Progress in Internal Medicine

Volume Factors in Body Fluid Regulation

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Notwithstanding the fact that much of modern physiology has concerned itself with the maintenance of constancy of the milieu intérieur, a definite lag persisted in the study and understanding of those factors regulating the normal volume and distribution of body fluids. Starling, with his rare insight, had early called attention to the fact that such control must exist,[200] and experiments supporting this idea were subsequently reported,[1,8] but the implications of the results—far ahead of the conceptual thinking of the time—fell upon soil unprepared for germination.

Historically, several factors contributed to the delayed growth of knowledge of fluid volume regulation. Measurements of body fluid constituents by the standard chemical methods are reported, in the language of chemists, as concentrations, and so accustomed have we become to this method of expression that students frequently find it difficult to associate a normal concentration with a highly abnormal amount of substance in a fluid compartment. Indeed, until recently, physicians have tended to equate normal hematocrits or "hemoglobins" (omitting the "concentration") with normal blood content or volume.

Secondly, while acute changes in plasma volume could be estimated from variations in concentration of plasma protein or hematocrit, the measurement of absolute volumes of the body compartments had to await the development of adequate dilution techniques, both chemical and physical.[49,73,112] Moreover, the errors of measurement of volumes or spaces of distribution, depending, in part, upon determinations of concentration, are, of necessity, larger. Experimentally, therefore, such changes, to be statistically significant, must be of greater magnitude. Since the bodily mechanisms for maintaining normal tonicity are more finely regulated in terms of amplitude and more efficiently governed with regard to rapidity of readjustment and since changes in tonicity must be prevented or overcome in order to validate the participation of volume factors, experimental demonstration of the latter has been rendered more difficult. Furthermore, prior to the advent of flame photometry, the determination of cation concentration was a laborious and time-consuming procedure relatively infrequently performed.

Lastly, the classic work of Verney on posterior pituitary antidiuretic hormone,[211] demonstrating the very fine control of tonicity and water excretion inherent in the osmoreceptor mechanism, tended to focus attention on the maintenance of fluid concentration somewhat to the exclusion of other regulation.

As late as 1937, Smith[196] wrote, "The kidney itself is not concerned with whether two or five liters of plasma are circulating in the vascular bed as long as that plasma has the proper composition. And this organ, in attempting to regulate the composition of the plasma, will frequently enlarge or reduce the volume of that fluid, and indirectly of the interstitial fluid, beyond physiological limits, and sometimes to fatal excess." Nevertheless, a somewhat tacit acceptance of

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the existence of volume regulation long preceded its experimental demonstration. As Borst [26] pointed out, the normal dependence of salt and water excretion on intake presupposes volume control, for if these are taken in equivalent quantities, there is no osmotic stimulus for excretion. Conversely, parallel losses of salt and water would not stimulate release of antidiuretic hormone. Or, as Peters succinctly put it, "The ultimate elimination of physiological salt solution is clear evidence that the volume of the body fluids is not a matter of complete indifference to the kidneys."[165] It has been known for some time that despite the importance of the plasma sodium concentration in determining urinary excretion, a high plasma sodium concentration due to the infusion of a hypertonic saline solution will result in greater urinary sodium output than an equally elevated plasma sodium level resulting from loss of water.[215] Similarly, in dehydrated persons, the urine is more concentrated and the flow smaller than in hydrated subjects receiving apparently supramaximal doses of vasopressin (Pitressin).[221]* In 1921, Adolph, noting that orally ingested hypertonic saline resulted in a more rapid water excretion than did isotonic salt, attempted to reduce a hypertonic diuresis by the intake of sufficient water to make it isotonic, and produced increased urine flow, an apparent volume effect.[1] When the converse was attempted, however, that is, water ingestion followed at the height of diuresis by salt, the water diuresis was inhibited.

Such earlier experiences, while not always fully explained by the investigators, prompted Peters to write, "It may well be the fulness of the blood stream which provokes the diuretic response on the part of the kidneys."[165]

* In this study, the urine concentrating ability was shown to depend, in part, upon plasma concentration. Therefore, the decreased concentrating power associated with plasma dilution or greater fluid volume permits more water relative to solute to be removed, a mechanism which protects fluid volume.

Salt Depletion

Since a fall or contraction of body fluid volume is a more frequent and serious threat to survival than a rise, the body's homeostatic mechanisms are more resistant to the former both in the promptness and rapidity of response. Moreover, since a decreased volume is more easily produced in the laboratory, some of the earliest experimental indications of volume regulation resulted from attempts to produce salt and water depletion.[113,146]

Ordinarily, salt loss per se would be expected to inhibit posterior pituitary antidiuretic hormone production, the resulting increased urine flow serving to reestablish the original plasma sodium concentration. When McCance [146] produced severe human salt depletion by means of combined low intake and excessive perspiration, water output was, in fact, high at first. However, following the loss during several days of between 3 and 4 kg. and equivalent sodium and associated contraction of the extracellular fluid volume, water retention ensued despite the low plasma sodium concentration.† Moreover, the ingestion of water failed to produce a normal diuresis, whereas salt administration led to increased urine flow. As McCance expressed it, "The body has begun to sacrifice its osmotic pressure to maintain its plasma and extracellular fluid volumes."

In addition to Kerpel-Fronius,[113] whose results in rabbits paralleled those of McCance, other investigators have since essentially corroborated the above findings. Employing peritoneal dialysis with glucose solution, Darrow and Yannet [42] and Bristol [27] produced acute salt depletion in dogs, and dogs and rats, respectively, and noted a markedly diminished diuretic response to ingested water. According to the latter, the degree of impairment appeared to be proportional to the fall in serum sodium concentration.

† The apparent anachronism of this observation disappears if the impaired ability to excrete water is regarded as primary to, and therefore responsible for, the hyponatremia.[155,223]

In relation to these experiments, another aspect of volume regulation became the subject of some attention. While impaired water diuresis tends to maintain body fluid content, any significant reversal of the contracted volume must depend upon fluid intake. As such, the spontaneous water ingestion or thirst of salt depletion became the center of considerable controversy. This will be discussed under thirst (see below).

A clinical counterpart of these experiments was studied by Leaf and Mamby,[124] who found that patients with Addison's disease and low serum sodium values excrete a concentrated urine and exhibit the usual impairment of water diuresis until the Addisonian state is corrected. The inadequate water excretion is not due to delayed intestinal absorption, for serum dilution occurs as during intravenous administration. In an effort to maintain volume, the already dilute serum is not protected against further dilution. Similar findings are encountered in congestive failure and following the administration of vasopressin. The authors concluded that contracted volume, as well as increased tonicity, may stimulate the release of antidiuretic hormone.

The importance of both volume and tonicity of the extracellular fluid in overcoming the circulatory impairment of salt depletion shock was demonstrated by Elkinton, Winkler, and Danowski.[57] Neither urea alone, which, by osmotic diuresis, restores tonicity at the expense of volume, nor dextrose, which expands the diminished volume while sacrificing tonicity, significantly improved circulatory function. However, when both substances were given together, or dextrose was followed by the administration of hypertonic saline solution, rapid return of normal circulation followed.

Water Depletion

Unlike the somewhat varying results obtained during experimental salt depletion, a definite consistency has characterized the investigations of water deprivation. In any renal effort to maintain tonicity during water loss or deprivation, increased salt excretion would be expected. Nevertheless, Kerpel-Fronius [113] observed that sodium and chloride virtually disappear from the urine of rabbits deprived of water despite a high and rising serum concentration. Potassium excretion, however, increases, and to a greater extent than is explicable by nitrogen loss and the potassium:nitrogen ratio of cellular fluid. Elkinton and Taffel [55] obtained similar results in dogs, with the total negative water balance considerably exceeding the extracellular water loss. Therefore, migration of water from cells occurs, and must depend largely upon osmotic factors, i. e., extracellular hypernatremia, an equivalent passage of potassium from cells, and cellular protein loss. The potassium migration, reflected in the increased excretion and attributed to a stress reaction, permits the cells to participate in minimizing the hypertonicity and shrinkage of the extracellular fluid compartment.[26] Similar potassium loss has been encountered in other stressful states involving decreased volume,[202] as well as during the intravenous administration of hypertonic saline to animals not deprived of water,[186] suggesting that the effect is either osmotic or related to local renal factors. Borst wrote, "The retention of sodium chloride and the increased excretion of potassium form . . . part of a regulating mechanism established for the purpose of restoring the normal filling of the arterial system by way of an augmentation of the total extracellular fluid and therefore of the blood volume."[26]

Similar studies in humans, conducted by Black, McCance and Young,[20,149] revealed little, if any, change in blood volume as estimated from the concentrations of hemoglobin, plasma protein, and hematocrit. The pattern of electrolyte excretion was similar to that previously described. The increased potassium and decreased sodium excretions were interpreted as a preferential body defense of extracellular fluid and plasma volume by the removal of supplementary cellular water. In these subjects, the renal hemodynamics remained normal, indicating that (1) water depletion does not involve

the same circulatory impairment as does salt depletion and (2) the decreased sodium excretion is a renal tubular effect.[149]

The bodily responses to excessive water loss, specifically the inverse relation between plasma cation concentration and urinary excretion, implies the existence of a prepotent stimulus for volume maintenance, one so basic that death may result from the increased osmotic pressure of the body fluids. These responses have been summarized by Welt and co-workers,[217] who point out that hypernatremia leads both to cellular dehydration and to release of posterior pituitary antidiuretic hormone. The former results in increased thirst and decreased insensible water loss and sweating,‡ while the latter produces water retention. Secondly, the contracted volume of all body compartments increases renal tubular sodium reabsorption and contributes further to antidiuretic hormone production. Thirdly, the increased plasma oncotic pressure associated with hemoconcentration further stimulates tubular resorption of both sodium and water.

Isosmotic Fluid Loss and Deviation

In the above experiments, the disproportionate loss of either sodium or water produced osmotic effects tending to complicate the picture, for despite responses which appear to be counter to the demands of osmotic equilibrium but compatible with volume control, indirect effects of osmotic stimuli are not eliminated. The removal of body fluids or administration of isotonic mixtures permits study of volume effects in the absence of significantly altered osmotic pressures.

For example, even mild bleeding results in prompt renal retention of sodium and water, the loss of 2.5 ml/kilogram producing a clear-cut fall in renal sodium excretion without measurable changes in cardiac output or glomerular filtration rate.[133] Evidently, prompt stimulation of tubular sodium reabsorption must occur. Isosmotic fluid loss of an equal or greater degree may also take place following external drainage of gastrointestinal secretions, extensive burns, and, in fact, during any major surgical procedure, as blood, sweat, and tissue fluids. Experimentally, a situation akin to fluid loss has been produced by sequestrating or trapping body fluid, without external loss, by such procedures as quiet standing and/or tilting, application of venous tourniquets, obstruction of the inferior vena cava, and other means.

While loss of fluid from the circulation is common to all the above experimental and clinical states, some (bleeding, burns) involve the additional loss of plasma protein, with varying effects on the plasma oncotic pressure. In all cases, however, plasma volume or the volume of effectively circulating blood is decreased. In experimental trapping or deviation of fluid by venous obstruction, this fall is not accompanied by a decrease in total extracellular fluid volume, since the trapped fluid is simply redistributed to the locally congested areas; the volume of actively (effectively) circulating blood is nevertheless diminished, while, at the same time, localization of a protein-poor transudate tends to increase the plasma oncotic pressure. Finally, common to all these states is a decreased venous return and its sequelae.

Following the loss or deviation of body fluid, even prior to other measurable hemodynamic changes, renal electrolyte and water excretion is diminished. When the circulatory volume or flow is further reduced and the cardiac output falls, arterial pressure is maintained by fairly generalized vasoconstriction. The kidneys, which normally receive approximately one-fifth of the cardiac output, in huge contrast to their size, suffer a disproportionately large decrease in blood flow, which readily falls to less than 25% of its original value.[121,171] Even under these circumstances, glomerular filtration is better protected as a result of increased efferent glomerular arteriolar constriction. More-

‡ Sweat loss, like other evaporative phenomena, is inversely related to the osmotic pressure of body fluids or is directly dependent upon vapor pressure which is reduced proportionately to the hypertonicity of the body fluids.[75]

over, the renal removal of many waste products is still carried on quite efficiently. However, in keeping with modern concepts of renal sodium excretion,[220] reduction of the filtered sodium load results in almost complete tubular reabsorption and the excretion of a virtually sodium-free urine. At the same time, water excretion is reduced, sometimes to an even greater degree,[65,152] the resulting highly concentrated urine suggesting posterior pituitary antidiuretic hormone release. The water retention serves to maintain the volume of body fluid.

The circulatory deviation above described has its clinical counterparts in edema or ascites formation of cardiac, hepatic, or renal origin, in secondary shock, and in the circulatory restriction of acute pericardial effusion[172] and chronic constrictive pericarditis.[63]

Quiet Standing and Tilting

Although the diminished urine flow upon assumption of the erect posture was observed at the turn of the century, few experiments were attempted to study quantitatively the effect of position on renal function until many years later. Bazett and co-workers[12] and Simpson[194] meanwhile demonstrated that urinary chloride excretion is increased by recumbency and falls on quiet standing, and Thompson and co-workers[210] called attention to the hemoconcentration in the passive erect position. White and co-workers, in 1926, attributed the greater urine flow of recumbency to increased pulse pressure and renal blood flow and more active glomerular function,[226] but Ni and Rehberg, making use of the latter's clearance concepts, explained the findings in more modern terms, including a fall in creatinine clearance (diminished filtration).[159]

The studies of Asmussen and co-workers[5] anticipated later work. They found that the ingestion of water while standing leads to plasma concentration, but when cuffs are applied to the lower extremities and inflated, water ingestion causes plasma dilution like that encountered following drinking during recumbency. They noted, too, that standing produces a decreased central venous pressure, poorer right atrial filling, and lower cardiac output. In these patients, the heart rate appeared to increase in an attempt to maintain cardiac output and arterial pressure. The antidiuresis observed during quiet standing is considerably modified or prevented by standing in water extending to the level of the heart, or by applying pneumatic cuffs to the legs. These workers, therefore, attributed the antidiuresis to a change in some function of the blood volume, the latter being related, in turn, to the distribution of the blood.

The problem was restudied by Brun, Knudsen, and Raaschou,[29] making use of present methods for measuring renal hemodynamics. With erect posture, the urine flow fell, and upon resumption of recumbency, it rose again, the increase beginning promptly, but requiring about an hour to reach the initial level. In the erect position, both the inulin and the iodopyracet (Diodrast) clearances fell significantly, the latter more so. Simultaneously, the heart rate and diastolic blood pressure rose as the increased peripheral resistance of general vasoconstriction became manifest. In some subjects, prolonged upward tilting of the head brought on collapse and syncope, followed by oliguria. At this time, the transfusion of their blood to other, normally hydrated persons and to one patient with diabetes insipidus led to a striking fall in the recipients' urine flows. The authors concluded that the antidiuresis of tilting is related not only to renal hemodynamic changes, but to the release into the blood of an antidiuretic substance which could be transferred. The rate of increasing urine flow following recumbency is reasonably similar to that encountered on abruptly discontinuing vasopressin administration.

The mechanisms underlying the changes in circulatory and renal function associated with tilting to the erect position have been further investigated in several laboratories.[58,79,98,164] From these and other studies,

evidence has accumulated that the decreased salt and water excretions, which universally occur, are mediated via separate mechanisms and are related to more complex circulatory functions than osmolarity or even plasma volume as such. Thus, there is no constant relation between sodium excretion and renal hemodynamics,[58] the former decreasing substantially in the absence of significant changes in the glomerular filtration rate.§ Iso-oncotic albumin does not prevent the antidiuretic effect, which therefore is not primarily due to a decreased plasma volume. However, the distribution of plasma or circulating blood in determining its circulatory effectiveness may be more far reaching in its consequences.

The role of fluid distribution relative to volume has been studied by Pearce and Newman,[164] who found that wrapping the legs with elastic bandages prior to standing prevents the fall in salt excretion, although antidiuresis occurs. The absence of the latter in patients with diabetes insipidus and its prevention by the ingestion of alcohol implicates the posterior pituitary antidiuretic hormone.[52,109,206]

The separation of the effects on water, as contrasted to salt, excretion led to attempts to trace other pathways, notably the adrenal cortex, to explain the antisaluresis. In adrenal insufficiency, the antisaluresis resulting from quiet standing is either much reduced or very transient.[215] Holland[98] compared the effects of head-up tilting with those of corticotropin (ACTH), cortisone, desoxycorticosterone glucoside, and vasopressin in normal subjects previously given a high salt intake. Of these, only vasopressin produced a fall in water output akin to that of tilting, and this was unaccompanied by a fall in salt excretion or eosinophile count. Neither cortisone, corticotropin, nor desoxycorticosterone glucoside administration resulted in decreased salt excretion within four hours; indeed, the latter brought about some chloruresis without a consistent change in sodium output. These results were interpreted as indicating that the antisaluresis of tilting is not dependent upon the mediation of the adrenal cortex.

The role of the adrenals in regulating tubular sodium reabsorption under various conditions, including postural changes and venous congestion, was investigated further by Rosenbaum and co-workers[183] in Addisonian patients on constant maintenance dosage. The fact that changes in sodium excretion occurred despite a constant glomerular filtration rate and plasma sodium level, or constant filtered load, established that variations in tubular sodium reabsorption do not require parallel changes in adrenal cortical activity. However, the variability of tubular response observed on cortisone therapy was much reduced in one patient on desoxycorticosterone acetate (Doca). The authors concluded that while the responses obtained may not be dependent upon any acute change in adrenal function, the ability of the tubules to modify their responses may require a maintained degree of corticoid activity. This is in accord with the results of Roemmelt and co-workers,[180] who found markedly diminished ranges of responses to salt and water loading in adrenalectomized dogs, although the loads were eventually removed.

That localized receptors may be instrumental in regulating the response to postural changes was suggested by Lusk and co-workers,[141] who found that the decrease in salt excretion following the assumption of the erect posture can be prevented by the application of venous tourniquets about the neck. The implications of this work will be discussed further (see below).

Venous Congestion

The experimental production of venous congestion, in sequestrating a fraction of

§ Differentiation should be made between the mathematical or statistical and biological "significance" of changes in glomerular filtration. The former is based upon an accumulation of the sources of error in the measurement. However, it is quite conceivable that statistically insignificant change in the glomerular filtration rate is physiologically significant in its effects. This is not susceptible to proof until the accuracy of measurement is increased.

the plasma volume and reducing the venous return, results in a series of changes in cardiovascular and renal function which have been intensely studied during recent years. In 1940, Ebert and Stead [48] demonstrated that the application of venous tourniquets to three extremities results in pooling or fall in plasma volume of 580 to 890 ml. This amount, about one-sixth of the blood volume, approximates that removed during phlebotomy and may be expected to be hemodynamically equivalent. Such venous occlusion, in addition, produces a significant increase in the extracellular fluid (inulin) space.[127]

Employing cardiac catheterization, McMichael and Sharpey-Schafer [151] found that venous congestion of the lower extremities is accompanied by a decreased cardiac output, which was attributed, in turn, to a fall in right atrial pressure. Warren and co-workers [213] corroborated the reduction in venous and right atrial pressure following pooling of blood in the legs.‖ Since they could demonstrate no consistent or significant changes in cardiac output, they concluded that the right atrial pressure of recumbent subjects is normally slightly in excess of that required to fill the ventricle, so that small decrements in pressure do not impede ventricular filling. Subsequently, Howarth and co-workers,[104] emphasizing the importance of the right atrial pressure in regulating ventricular filling and therefore the cardiac output, pointed out that in patients in congestive failure, already on the "wrong" or falling output side of the Starling curve, experimental lowering of the right atrial pressure (venesection) results in an increase in cardiac output. This finding is of interest in the light of the observation of Judson and co-workers,[110] who found that whereas normal subjects exhibit a fall in cardiac output on venous congestion or phlebotomy, patients in congestive failure invariably demonstrate a slight, but significant, rise.

‖ The right ventricular end-diastolic and pulmonary arterial pressures are also decreased.[60]

Employing renal clearance measurements for studying renal function, Fitzhugh and co-workers [65] restudied the effects of venous congestion and found that both the cardiac output and renal hemodynamics fall and rise promptly with application and removal, respectively, of the tourniquets.¶ The excretion of sodium falls markedly and too quickly to be readily explicable on the basis of adrenal cortical stimulation; moreover, on release of the tourniquets, its return to control values is slower than that of the cardiac output or renal hemodynamics. Water excretion is slowest to return to normal, suggesting the superimposition of antidiuretic hormone activity. In order to establish whether the decrease in cardiac output may be the result of a diminished effective circulating volume, or secondary to the congestion experimentally produced, one liter of isotonic saline solution was rapidly injected intravenously while the tourniquets were in place. Despite the resulting increased circulatory and venous congestion, the cardiac output rose above its control level with simultaneous increase in renal hemodynamics. Local venous congestion was therefore not primarily responsible for the previous fall in cardiac output. However, to the extent that the principal effect of the saline infusion is to expand the effective blood volume, flow, or function thereof, the previous falls may be attributed to volume effects which, the authors believe, are exerted via the venous return or right atrial pressure.

Extensive study of bodily responses to venous congestion in Wilkins' laboratory [109, 110, 228] indicated that the observed falls in renal hemodynamics and sodium and water excretion on application of tourniquets is generally similar to those previously described. The effect on urine flow is greatest after 10 minutes of congestion, the flow falling to one-tenth of its previous level. Electrolyte excretion falls less, and so uri-

¶ As described, the fall in renal blood flow considerably exceeds that of filtration, suggesting intrarenal adjustment to maintain glomerular function.

nary concentration rises. The hematocrit and plasma protein concentration rise due to the transudation of plasma ultrafiltrate. As a rule, the blood pressure remains fairly constant and the heart rate increases slightly, although in severer reactions with marked antidiuresis, and presumably pronounced fall in cardiac output, decreases in blood pressure are associated with very rapid heart rates. On release of the cuffs, following transient further reduction in urine flow, renal hemodynamics, and sodium excretion, these functions return to their control values, urine flow being the last to do so.

These effects are not due to local factors in the lower extremities, since similar results are obtained on congestion of the arms. Nor are postural influences responsible, since the subjects remained supine throughout the procedure. Moreover, as in the experiments involving head-up tilting, one patient with diabetes insipidus exhibited no antidiuresis on venous congestion, although sodium excretion fell, indicating both the separation between the two functions and the normal participation of posterior pituitary antidiuretic hormone.[108] The dichotomy was also demonstrated by experimental mannitol osmotic diuresis during venous occlusion. Normally, the diuresis resulting from adequate intravenous mannitol administration results in considerably increased excretion of both salt and water.[79,187,229] However, when venous occlusion is superimposed,[109] the high urine flow continues but sodium excretion falls, the volume and renal osmotic effects of the mannitol being inadequate to counteract the increased tubular reabsorption of sodium.#

In hypertensive patients treated by splanchnicectomy, venous congestion prior to and following surgery produces similar effects, thereby eliminating neurogenic influences from responsibility for the decreased water and sodium excretion and reduced renal hemodynamics encountered.[109] These changes, however, can be prevented in normal subjects by the administration of a large transfusion (1000-1500 ml.); smaller amounts of blood are ineffective. Thus, when adequate blood is infused during application of the tourniquets, neither sodium nor water excretion falls, indicating, as did the saline infusion of Fitzhugh and co-workers,[65] that the effectively circulating blood volume, rather than venous distention or edema formation, is responsible for the observed changes in renal function. The significance of volume factors is further highlighted by the observation that compression of the lower extremities by antigravity, or G, suits during application of the tourniquets prevents all the effects previously observed, presumably by preventing fluid transudation. These data, moreover, rule out the possibility that the antidiuresis is due to any discomfort or tissue ischemia.

When similar experiments are performed in cardiac patients, the consistent falls in sodium and water excretion observed in normal subjects are not encountered, presumably because of the different directional changes in cardiac output.[110] Whereas the cardiac output of all of five normal subjects fell during venous congestion or phlebotomy without change in the normally low right ventricular end-diastolic pressure, the cardiac output of the patients in congestive failure rose slightly, while the originally elevated right ventricular end-diastolic pressures fell. Antidiuresis was associated with a fall in cardiac output, but was not necessarily related to changes in right ventricular pressure. These results, reminiscent of those of Howarth and co-workers [104] and compatible with the latter's interpretation, led the authors to conclude that so-called "volume" receptors are, in essence, pressure receptors, while the urinary changes are mediated via humoral or intrarenal regulatory effectors.

It is likely that the renal osmotic effects of mannitol, apart from its cellular dehydrating action, by diminishing proximal tubular water reabsorption, inundate the distal tubules to an extent whereby, even under maximal antidiuretic hormonal stimulation, much water remains unresorbed. Proximal tubular sodium reabsorption meanwhile remains unimpaired.

Experiments physiologically comparable to those involving venous tourniquets were performed by obstructing the inferior vena caval flow. When Hwang and co-workers [105] partially ligated the inferior vena cava above the renal veins, the resulting increased peripheral and renal venous pressures were associated, at first, with decreased renal hemodynamics and reduced excretion of water and electrolytes. Subsequently, however, despite the continually elevated renal venous pressure, the renal hemodynamics and sodium excretion returned to normal levels. Similar results were obtained by Blake [22] and Selkurt [90,188] and their colleagues by partial ligation of a renal vein. In these studies, the falls in sodium and water excretion exceeded the decreases in renal hemodynamics.* That the changes reported by Hwang were not due solely to increased renal venous pressure should be apparent from the experiments on venous congestion and tilting already alluded to, as well as the studies of Farber and co-workers,[61] who occluded the superior vena cava and inferior vena cava, both above and below the entrance of the renal veins, by means of balloons attached to venous catheters. They found that superior vena caval obstruction resulted in decreased water and sodium excretion despite insignificant changes in renal hemodynamics. They observed that inferior caval obstruction below the renal veins produces more variable and therefore less significant changes in salt and water excretion than occlusion above the renal veins, which involves a much greater degree of interference with venous return. The heart rate, blood pressure, electrocardiogram, serum electrolyte concentrations, filtration fraction, hematocrit, and plasma protein concentration exhibited no significant changes, the two latter indicating absence of hemoconcentration and change in blood volume. However, a decreased cardiac output or effectively circulating blood volume might have underlain the findings, the authors attributing the "volume" effect to altered stretch or tension of the vascular walls.

A somewhat different form of interference with venous return results from experimental pericardial lesions. The production of acute pericardial effusion depresses the cardiac output despite the increased venous pressure and results in decreased renal hemodynamics † and an even greater fall in sodium excretion.[172] Nevertheless, in chronic pericarditis with effusion,[63] in which the rise in venous pressure (preceding the hypervolemia) helps maintain the cardiac output, fluid retention occurs despite the normal resting cardiac output and renal hemodynamics. Increased tubular sodium reabsorption is stimulated in the face of expanded extracellular fluid and plasma volume, although the effectively circulating volume may be depressed and the fluid distribution abnormal.

The role of altered fluid distribution and stretch of the vascular walls referred to [61] is well illustrated by recent experiments on arteriovenous fistulae.[59,67,97] These are associated with a high total blood flow or cardiac output, the efficacy of which is questionable, since much of the increase bypasses the capillary bed and contributes nothing to circulatory function. The blood, especially the venous, volume is increased with elevated pressures in the large veins, right atrium, and pulmonary circulation. When an arteriovenous fistula is acutely closed, the cardiac output falls promptly, renal hemodynamics are unchanged, central venous volume and pressure fall, but urinary sodium excretion rises.[59] Conversely, opening an arteriovenous communication,

* As mentioned by Selkurt,[189] the proportional changes in glomerular filtration rate and renal plasma flow rule out the possibility that the elevated renal venous pressure is responsible for the more marked fall of the renal plasma flow encountered in congestive failure. The increased tubular sodium reabsorption in the ipsilateral kidney indicates a local effect (in contrast to hormonal) of the increased renal venous pressure.

† However, the renal fraction (that portion of the total cardiac output supplying the kidneys) is increased, as in the acute congestive failure produced by pulmonary artery constriction.[38]

while increasing the cardiac output, decreases sodium excretion.[25,59] ‡ These changes occur far more rapidly than can be accounted for by changes in blood volume, and, in terms of Starling's law, are in the reverse direction with regard to central venous filling behind a normal myocardium. However, the changes in sodium excretion do tend to parallel the degree or duration of arterial distention or filling, and thereby the mean arterial pressure and its influence on vascular stretch receptors.[59] It is difficult, however, to relate mean arterial pressure to the changes in electrolyte excretion, since the kidneys, at least in isolated perfusion experiments,[189,191] maintain quite constant renal hemodynamics, urine flow, and sodium excretion over a relatively wide range of mean arterial pressure. Conceivably, then, volume effects may be mediated by vascular receptors on the arterial side and be independent of local pressure changes in the renal circulation. Insofar as renal sodium excretion is independent of central venous pressure or ventricular filling and absolute cardiac output but tends to parallel vascular filling, this work suggests that the initiation of events of congestive failure, the inadequacy of cardiac output relative to metabolic needs, may be mediated via vascular pressure or tension receptors, perhaps in the distal parts of the arterial system, the "needs" being made known to the body and kidneys via vascular filling.

Fluid Distribution

Early studies on volume responses stimulated interest in the nature and location of those receptors through which the effects are mediated. It became readily apparent, since it was assumed that these receptors are discrete structures, that the problems of fluid volume were considerably intertwined with those of fluid distribution within the body,[167] both with regard to any single physiological compartment and among the various spaces. As a result, experimental procedures were designed to modify the volume of one compartment with minimal changes in volume and concentration elsewhere.

The Starling concept of fluid equilibration laid considerable emphasis on the role of the oncotic pressure in maintaining the plasma volume. Following application of this principle to clinical conditions, attempts were undertaken to counteract the salt and water retention and edema of hypoalbuminemic states. Hartmann employed intravenous acacia in nephrotic children and was able to remove considerable fluid.[93] Subsequently, employing dye-dilution methods, Lepore studied the changes in plasma concentration and volume following the administration of acacia and showed that while the plasma oncotic pressure remains fairly constant, the plasma volume rises considerably due to the migration of interstitial fluid into the blood stream. The resultant diuresis was attributed to an acute increase in plasma volume acting via the glomerular filtration rate.[126]

Goudsmit and co-workers studied the renal effects of acacia in both normal dogs [83] and nephrotic patients.[82] In the former, despite an unchanged glomerular filtration rate and a fall in serum chloride concentration secondary to hemodilution, a marked increase in urinary chloride excretion was consistently observed, largely independent of the urine flow. The results in the nephrotic patients were essentially similar, although larger water outputs were usually obtained. These findings represented early evidence of a volume effect in the face of decreased tonicity.

The preparation of stable concentrated human serum albumin made available a more physiological substance for increasing the plasma oncotic pressure. Its wide use,

‡ In a more recent study,[97] the acute opening of an arteriovenous fistula in anesthetized dogs resulted in a fall in renal hemodynamics as well as electrolyte excretion. It may be that the size of the communication determines whether the additional changes occur. In acute experiments, the blood volume may be insufficient to maintain the venous return necessary to sustain the increased cardiac output until such time as the sodium retention has increased the plasma and blood volume.[97]

both in normal subjects and in hypoalbuminemic, edematous patients, as a tool for experimentally controlling fluid distribution provided interesting data on the nature of the renal responses to volume effects. In normal subjects, albumin produces a slight increase in glomerular filtration rate and a larger rise in renal plasma flow.[31] When given in concentrated (25%) solution, it results in a reduced renal excretion of salt and water without significant change in filtration rate or serum electrolyte concentration and despite a marked increase in plasma volume.[78,170,216] § However, isooncotic albumin, which, unlike the hypertonic solution, increases the plasma volume at no expense to the interstitial fluid volume, causes increased salt and water excretion.[216] These findings appear to relate renal excretion not to the plasma or blood volume but to the interstitial fluid volume, since the latter falls during hypertonic, but not isotonic, albumin administration.

The importance of the interstitial fluid volume is even more clearly exemplified by the results of albumin administration to patients with nephrotic syndrome. Cargill showed that the renal hemodynamic changes were more pronounced in nephrotics[31]; others also reported a significant rise in glomerular filtration rate following infusions of albumin.[50,135,162] In these patients, the renal hemodynamic changes were consistently accompanied by increased excretion of sodium and water on administration of adequate amounts of either hypertonic or isotonic albumin. The degree of diuresis did not appear to depend upon the increase in plasma volume or albumin concentration, but seemed to correlate with the amount of edema already present.

These results would appear to implicate the interstitial fluid volume as determining the renal response to albumin administration. If the plasma volume were the critical factor, normal subjects, rather than diminish their output, would respond with greater diuresis; if the change in plasma volume were largely responsible, then the response would be similar, per gram of albumin given, on hypertonic and isotonic administration. However, large extracellular fluid volumes are encountered in many clinical conditions with minimal salt excretion. The authors therefore interpret the different responses of normal and nephrotic subjects as follows: Because of the low plasma and high interstitial fluid volume of the nephrotic, the relative increase in plasma volume is greater, stimulating sodium excretion. Simultaneously, the large reservoir of interstitial fluid, by reducing the magnitude of increase of plasma oncotic pressure, thereby lessens the stimulus for sodium retention.‖ Since, in nephrotics, tubular sodium reabsorption is already maximal, further decreased excretion is quite unlikely, while the stimulus to water diuresis of the increased plasma volume is unimpeded.

The mechanisms underlying the above renal responses to human serum albumin administration have been sought to little avail. The essentially normal antisaluretic response following hypertonic albumin in an Addisonian patient on constant steroid dosage[216] would appear to rule out altered adrenal cortical function. However, if one

§ Of several investigators, only Elkinton and co-workers[88] noted increased excretion of sodium following the administration of concentrated albumin to normal subjects. The reasons for this discrepancy are not clear, but in view of their finding an associated increased potassium and decreased chloride excretion, it should be borne in mind that salt-poor albumin contains 155 mEq/liter of sodium as bicarbonate. The kaliuretic effect of bicarbonate is well known.[177]

‖ Since hemoconcentration usually results from fluid transudation or loss, an increasing oncotic pressure is interpreted by the body—or some receptor—as a contraction of plasma volume,[216] and is followed by an effort to retain fluid by means of increased renal tubular reabsorption. This response is sufficient to overcome the opposing tendency inherent in the increasing plasma volume. It is therefore not incongruous that the two processes, (1) hypoalbuminemic edema formation, with decreasing plasma oncotic pressure and increasing interstitial fluid volume, and (2) hypertonic albumin infusion involving increasing plasma oncotic pressure and decreasing interstitial fluid volume, both stimulate increased tubular reabsorption of sodium.

may analogize from the experiments of Rosenbaum and co-workers [183] (see above) involving postural changes in Addisonian patients on maintenance therapy, it may well be that while fluctuating adrenal cortical activity is not essential to the response, the ability of the tubules to vary their function may nevertheless require some steroid influence.

The decreased water excretion following concentrated albumin administration is probably not related to posterior pituitary antidiuretic hormone, since it is observed in patients with diabetes insipidus and is accompaned by a fall in urinary sodium concentration.[170] The latter, in fact, suggests that the decreased urine flow is secondary to increased solute reabsorption. However, the more pronounced antidiuresis unaccompanied by antisaluresis associated with more rapid albumin administration may imply the superimposition of an antidiuretic hormone effect. An explanation for the antidiuresis suggested by the authors, namely, enhanced tubular water reabsorption due to increased plasma oncotic pressure in the peritubular capillaries, appears unlikely to me. The increase in oncotic pressure as blood traverses the glomeruli to reach the tubular vessels is directly proportional to the filtration fraction, since the higher percentage of the renal plasma flow filtered the greater is the protein concentration in the unfiltered residue. Since the filtration fraction is probably reduced as a result of concentrated albumin administration, antidiuresis on this basis appears improbable. It is, however, conceivable that the greater diuresis encountered in nephrotic, as compared with normal, subjects following concentrated albumin, is, in part, due to the fact that the tubular albuminuria of the former results in a smaller than normal difference in oncotic pressure between the tubular lumen fluid and that of the peritubular capillaries, thereby retarding water reabsorption.

The more recently developed plasma expanders have effects on salt and water excretion akin to that of concentrated albumin. Dextran, while expanding the plasma volume, produces salt and water retention; subsequently, the salt is lost during postdextran diuresis. During dextran administration, both the plasma protein concentration and, in some cases, even the total circulating plasma protein, fall.[107]

The effects of independent salt and water deprivation and the apparently paradoxical osmolar effects suggesting the existence of mechanisms for maintaining fluid volume have been alluded to. Similar attempts to dissect volume and distribution effects from those of concentration have been carried out employing salt solutions of varying concentration administered under a wide range of conditions. Studies involving the administration of hypertonic saline solutions have consistently resulted in increased flow of a relatively dilute urine despite the physiologically adequate stimulus for posterior pituitary antidiuretic hormone release. Baird and Haldane,[8] in 1922, fed a highly concentrated mixture of sodium chloride and bicarbonate, obtaining increased urinary excretion of chloride and water. When this was followed shortly by the ingestion of 2.5 to 3 liters of water, a water diuresis ensued despite the presence of excessive salt concentration in the body. That volume influences underlay this response was indicated by the fact that a smaller water intake was without effect. This experiment in essence, but employing intravenous hypertonic saline, was repeated years later with similar results.[17] The diuresis following the ingestion of water was delayed, but occurred while the plasma sodium level was higher than the control values. Moreover, since the diuresis was hypotonic, it was accompanied by a rising plasma hypertonicity.

Baldes and Smirk [9] noted that the slow fall in plasma osmotic pressure resulting from low sodium intake produces no diuresis, whereas the acute fall following water ingestion is followed by marked diuresis. Ignoring the effects of volume, they concluded that the rate of change in osmolarity, rather than its magnitude, determines the diuretic response. However, as pointed out, dehydrated, as contrasted to

normal, subjects, after drinking a liter of water, despite a relatively greater decrease in osmotic pressure, have smaller diureses.

The use of isotonic, rather than hypertonic, saline in the hands of most,[23,24,155,204] though not all,[39] investigators has given results consistent with the participation of volume factors. In 1900, Thompson[209] noted that 0.9% saline given to dogs produces a large water diuresis with no increase in chloride excretion until the flow has subsided. Blomhert,[23] a half century later, reported that normal recumbent subjects receiving isotonic saline orally or intravenously exhibit a "water" diuresis. Strauss and co-workers[204] obtained similar results and attributed the diuresis to inhibition of antidiuretic hormone because of the fall in electrolyte concentration. These investigators stressed too that the much diminished or absent response in sitting, as contrasted to recumbent, subjects implies that the distribution, as well as the magnitude, of the increased volume determines the response. Murphy and Stead[155] infused normal saline very rapidly (20-30 ml/kilogram in 25-40 minutes) and obtained a prompt "water" diuresis followed by a precipitous fall in urine flow associated with increased sodium concentration. This diphasic response was attributed to initial dilution of circulating antidiuretic hormone, followed subsequently by additional release as a result of the plasma hypertonicity. Indirect evidence of such secondary posterior pituitary discharge lay in the fact that at this time intravenous vasopressin (1 milliunits/kg.) had little or no antidiuretic effect. Presumably, this resistance is due to already maximal antidiuretic hormone activity, although the existence of a higher distal tubular sodium load may be partly responsible. Concerning the latter alternative, it is of interest that the flow during this second phase is much greater than that of the subject receiving water and vasopressin.¶ The contribution of the posterior pituitary was further illustrated by Tarail and Logsdon,[208] who compared the renal responses to hypertonic saline of normal subjects with those of patients with diabetes insipidus. The latter excreted the sodium at a normal rate but with an associated greater loss of water, so that the hypertonicity of the plasma persisted considerably longer.

An interesting demonstration of volume regulation was carried out by Papper and co-workers[163] by comparing the renal sodium excretions following the infusion of 338 mEq. of salt, given as isotonic (0.9%) and hypertonic (5%) solutions. Despite a significant increase in serum sodium concentration following administration of the more concentrated saline, in six of eight subjects the natriuretic response following the isotonic saline was equal to or greater than that associated with the hypertonic solution. Since, in these experiments, the creatinine clearances were quite constant, the more pronounced natriuresis associated with the greater volume of isotonic saline occurred in the face of a smaller tubular sodium load.

Nevertheless, it should not be inferred from the foregoing that the volume effects are all-pervasive. Considerable experimental evidence exists for the important influence of tonicity. The administration of 10% salt, a solution more hypertonic than the most concentrated urine of which the animal is capable, results in a large diuresis of lower specific gravity, the organism protecting the tonicity or composition of the extracellular fluid at the expense of its water content or volume.[148]# However, under these conditions, the highly elevated

¶ The importance of the sodium load in determining the degree of vasopressin antidiuresis has been stressed by Smith,[197] who defines water output at any moment as a function of antidiuretic hormone activity and sodium load.

Since urea, unlike saline, rapidly enters cells, the fact that hypertonic urea acts like the concentrated saline tends to rule out cellular dehydration. Consequently, the body's response is a defense of over-all osmotic pressure.

osmotic pressure poses a greater and more immediate threat than does the resultant loss of fluid volume. The experiments of Darragh and co-workers [41] also emphasize the importance of tonicity. Noting that most clinical hypotonicity or hyponatremia is associated with falls in volume, these workers produced hypotonicity without contraction of the body fluids by positive water balance or intravenous dextrose (5%) in water plus vasopressin and followed this with isotonic or hypertonic sodium loading. Dilution of the serum electrolytes was found to result in reduced electrolyte excretion. This attempt to maintain tonicity by sodium retention was believed to be mediated either by a decreased effective extracellular osmotic pressure or cellular overhydration. Because the changes in filtered sodium were minimal and not readily related to sodium excretion, tubular sodium reabsorption was believed to be the effector.

While increased urine flow following isotonic saline may appear not unreasonable, since volume effects are not counteracted by those of tonicity, the increased flow resulting from hypertonic saline, despite the stimulus for antidiuretic hormone release, appears paradoxical and implies the superimposed effects of additional, nonosmotic factors. Hypertonic saline, distributed throughout the extracellular fluid, tends to draw water from the cells. The increased extracellular fluid volume and/or cellular dehydration inhibits proximal tubular reabsorption of sodium and chloride, thereby forcing the antidiuretic hormone to operate against a larger electrolyte load. Since urine flow is a function of antidiuretic activity and the electrolyte load with which it must contend,[197] hypertonic saline produces the excretion of as much additional water as may be required for the extra load. This explanation is supported by studies both in patients with diabetes insipidus [208] and in those with edema.[80] The latter, by diluting the administered sodium throughout a much larger space, exhibit smaller changes in extracellular fluid tonicity, none or little migration of water from cells, and therefore less increase in extracellular fluid volume. Changes in tubular sodium reabsorption are minimal, so that even slight antidiuretic hormone activity due to minimal hypertonicity exerts its effects unhampered.

In addition, sodium excretion is regulated by intrarenal influences as noted in experiments involving intrarenal arterial injections [77] and salt loading.[85]

Following the administration of hypotonic salt solution, increased flow of a dilute urine may be anticipated purely on the basis of inhibition of antidiuretic hormone release—a smaller water diuresis, so to speak. In fact, mixed osmotic and volume effects are encountered, as demonstrated by Strauss and co-workers,[205] who infused hypotonic saline (112 mEq/liter), thereby decreasing the concentration of sodium and chloride while increasing the extracellular fluid volume. Decreased tonicity, in the absence of significant volume changes, has been shown to diminish sodium excretion. Nevertheless, all recumbent subjects (but not those sitting) exhibited increased sodium excretion by increasing both the urine flow and its sodium concentration. During the procedures, the filtration rate was unchanged, and the plasma sodium level fell. The increased sodium output therefore coincided with a decreased filtered sodium load. Therefore, in terms of sodium excretion, volume effects on tubular function superseded the osmotic. Moreover, the mediation via cephalic structures was strongly suggested.

The effects of osmotic diuretics, like albumin, acacia, and the plasma expanders, have been discussed. Unlike these, other osmotic diuretics have been employed to study the effects of fluid distribution on volume regulation. The latter have a larger volume of distribution, which includes the extracellular fluid (mannitol) or total body water (urea). Further complications arise from the fact that they migrate at varying rates, dextrose, for example, entering cells slowly, and by their rapid excretion, for in the kidneys, their limited reabsorption and consequent high tubular luminal concentration produce renal effects independent of

their influences on body fluid volume.[77] However, most osmotic diuretics, in drawing water into the extracellular compartment, dilute the electrolytes, and thereby provide a more rigorous test of volume effects, similar to that of the infusion of hypotonic saline solution.

Seldin and Tarail,[187] studying the effects of hypertonic mannitol, dextrose, and urea, found that while all produce a greater saluresis in hydrated than in hydropenic subjects, the absolute salt excretion following urea is much less than that resulting from mannitol or dextrose. Indeed, in hydropenic normal subjects, urea causes a diminution of urinary salt output. The difference between urea and the sugars was attributed to the latter's slowness to enter cells, thereby exerting a greater effective * osmotic pressure of the extracellular fluid. The resultant migration of water from the cells, or cellular dehydration, reduces renal tubular sodium reabsorption.[84] Urea, on the other hand, enters cells rapidly, and so cellular hydration remains intact. However, the same differences in distribution result in the sugars' greater expansion of the extracellular fluid volume. Since the plasma electrolyte concentration is reduced, the greatly increased urinary salt excretion appears to be adapted to the extracellular fluid volume changes rather than to its electrolyte concentration. Secondly, whereas intravenous hypotonic saline given to seated normal subjects produces only a slight saluresis despite the increased extracellular fluid volume, hypotonic mannitol causes a marked increase in salt excretion.[229] Since overhydration is maintained and no contraction of the intracellular fluid compartment occurs in these experiments, and since sodium excretion rises very promptly, that is, before the extracellular fluid volume can have changed measurably, the mannitol effect is, at least partly, due to still other influences. Thirdly, the increased salt and water excretion by the ipsilateral kidney directly following injection of mannitol into the renal artery [77] is clear-cut evidence of local effects unrelated either to cellular dehydration or extracellular fluid volume. Urea, incidentally, produces similar local effects.

When the above experiments were repeated in edematous patients with congestive heart failure or hepatic cirrhosis, neither the osmotic diuretics nor hypertonic saline caused any natriuresis, the local renal effects having been unable to overcome the already conditioned, powerful, sodium-retaining mechanisms.[80] It is probable that the large extracellular fluid volume of these patients diluted, in part, the effect of these diuretics.

Volume Expansion

While fluid depletion or loss has been studied more extensively, in accordance with its greater incidence and threat to survival, the experimental production of abnormal increases in fluid volume has led to interesting data on the nature of some responses.

The simplest means of increasing rapidly the body fluid content—the parenteral administration of salt—has been discussed. The addition of water, which simultaneously decreases tonicity as it increases volume, has also been attempted. On forced water ingestion, there may occur early some [203] or no increase in salt excretion despite a positive balance of several liters. By inhibition of antidiuretic hormone, a highly dilute urine is excreted, much of the load being thereby rapidly removed. In addition, the water ingested is rapidly diffused throughout the entire body water,[51,96,123] † so that

* Relative to the intracellular osmotic pressure.

† This conclusion is based upon the fact that on administering water to nephrectomized (or vasopressin-treated) animals, or giving hypertonic solutions, the volume of distribution or of participation of water, calculated from the degree of plasma dilution or concentration, corresponds well with the total body water based on deuterium oxide measurements. These findings have been extrapolated to imply that the cells act as perfect osmometers, absorbing sufficient water to maintain osmotic equilibrium, in opposition to the findings of Robinson,[170] Opie,[161] and Conway,[87] and to the proponents of osmotically inactive intracellular base.[86] Actually, it is conceivable that even if sufficient water is absorbed to maintain a normal difference in concentration or osmotic pressure between cellular and extracellular fluid, a figure approximating total body water may be obtained.

the increase in extracellular fluid volume is much smaller than that following saline or mannitol and is relatively no greater than the expansion of intracellular fluid volume, which tends to promote tubular sodium reabsorption. Such general increase in volume and dilution may stimulate competing mechanisms.

However, as demonstrated repeatedly, despite a high continued fluid intake the urine flow falls,[86,89,111] and in dogs there is an associated decrease in serum chloride concentration without increase in urinary chloride excretion.[86] This is probably due to the migration of salt into the intestinal lumen. McCance and Widdowson, arguing from their observation of impaired water diuresis in salt-depleted subjects, suggested that this fall in urine flow is due to sodium depletion.[147] Bristol later stated that the impaired diuretic response of salt-depleted dogs and rats is proportional to the fall in serum sodium level.[27] The importance of the availability of solute for the maintenance of water diuresis was demonstrated by the more thorough studies of Rosenbaum and co-workers,[182] who showed that (1) the steady decline in sodium excretion is greater than that of water, (2) higher levels of diuresis are encountered at higher previous salt intake, (3) the increased sodium output on the assumption of recumbency, after prolonged sitting and antidiuresis, is accompanied by increase in urine flow, and (4) the administration of solute during declining diuresis is followed by increasing urine flows, the changes correlating most closely with those of sodium excretion. Thus, water given at those times of day when sodium excretion is greatest produces the largest peak responses. Moreover, the only successful means of maintaining maximal water diuresis for more than a few hours involves measures which sustain electrolyte excretion. Even in diabetes insipidus, the urine flow falls with decreased solute load.[18,28,190,231,233]

A similar relation between electrolyte excretion and urine flow has been noted by others.[21,91,118,120] Black and Thomson[21] studied day-to-day changes in sodium and water excretion in patients with and without vasopressin. While large variations were encountered, the sodium output bore no relation to vasopressin, and the sodium balance was not influenced by water excretion as such during water diuresis or in diabetes insipidus. However, the relationship between the urine volume and concentration suggested that electrolyte excretion is an important determinant of the urine volume. Halmágyi[91] noted the relationship between chloride and water excretion, but, ignoring the findings during water diuresis, concluded that the chloride output depended upon that of water. In any event, the diluted body fluids during forced water intake exert a stimulus akin to that of salt depletion with resultant impaired diuresis.

The electrolyte-depleting effect of water, apart from loss into the intestinal lumen prior to water absorption, is due to the inability of the kidney to excrete a urine below a certain minimal concentration (60 mOsm/liter).[114] When the electrolyte load is insufficient to maintain this level, additional tubular water reabsorption occurs. On continuing to force water beyond the development of oliguria, water intoxication ensues, its symptoms (nausea, vomiting, convulsions, etc.) completely obliterating the more subtle manifestations of volume mechanisms.

Because of these secondary effects, vasopressin has been employed in studies endeavoring to increase body fluid volume, the water so retained being distributed proportionately throughout the body water.

Leaf and co-workers[122] administered vasopressin for two to four days to normal subjects on a low sodium diet. When this was accompanied by a relatively high water intake, a progressive, large increase in urinary sodium and chloride excretion occurred, associated with some increase in the glomerular filtration rate. Similar vasopressin dosage during low water intake, insufficient to cause significant positive water balance, failed to bring about such saluresis, indicating that the water retention and ex-

pansion of body fluid volume, rather than vasopressin itself, is responsible. The high sodium output, occurring during low and falling serum sodium concentrations, indicates that the levels were no longer adequate stimuli for renal sodium conservation, having been overcome by the expansion of fluid volume. Since, in these studies, both corticotropin (ACTH) and low sodium intake tended to prevent the natriuresis, the renal tubules were evidently capable of further sodium reabsorption.

Similar, but more prolonged studies were performed by Weston and co-workers [224,225] in normal subjects on low and normal sodium intakes and on 2000 to 3000 ml. of fluid daily. Water retention, as evidenced by oliguria, weight gain, and fall in serum sodium concentration, was followed by sufficient sodium and chloride excretion to produce an osmotic diuresis. On discontinuing vasopressin, profuse water diuresis occurred with weight loss to below the control levels by amounts corresponding to the sodium loss. At this time, although serum electrolyte and total solute concentrations were below control levels, urine volume remained low. Gradually, thereafter, salt retention slowly and according to intake—and not to water diuresis—brought the serum concentrations back to control levels. Volume effects predominated, therefore, during both expansion and contraction of body fluid content. Measurements of renal hemodynamics during the natriuretic phase or "break-through" revealed highly elevated glomerular filtration rates and, in subsequent studies, considerable increases in extracellular fluid volume (inulin space). In these studies, neither low sodium intake nor corticotropin prevented the natriuresis and secondary osmotic diuresis. In fact, the saluresis during vasopressin administration occurred during eosinopenia and other evidences of adrenal cortical discharge. The latter may have contributed to the increased glomerular filtration. (Similar studies, published more recently from Venning's laboratory, will be discussed under "Aldosterone.")

When cardiac patients in congestive failure and on low sodium diets were similarly studied with vasopressin, despite the already increased fluid volume and superimposed water retention, the saluresis failed to occur. Instead, the accumulation of water intensified the failure so that it became necessary to discontinue the vasopressin.

Recently, Werkö and co-workers [218] acutely increased fluid volume by rapidly (25 ml/minute) infusing dextrose in water into normal subjects and patients with mitral stenosis. The former exhibited a prompt, marked diuresis which prevented fluid accumulation, no change in sodium excretion, and a slight increase in renal hemodynamics. The diuretic responses of the cardiac patients were more variable, but in those who were apparently less severely decompensated, the impaired excretion of water and consequent increase in volume was associated with a significant, sustained increase in sodium excretion and renal blood flow which at times reached normal levels. In these subjects, the cardiac output and pulmonary arterial pressure were increased.

Harris and co-workers [92] gave vasopressin to normal and cirrhotic subjects and found that the fall of serum sodium concentration gives rise to increased urinary corticosteroid excretion; if the hyponatremia is prevented, no urinary corticoid response occurs. Since the decrease in serum electrolyte concentration is inextricably associated with expansion of fluid volume, it would appear that the volume regulation or natriuresis of normal subjects observed by Leaf and Weston is mediated via the adrenal cortex.

Sustained experimental expansion of the extracellular fluid volume was attempted by Wesson and co-workers [219] in dogs by infusing saline at a rapid rate then rapidly reinjecting fluid approximating the volume and composition of the urine excreted, thereby maintaining the renal hemodynam-

ics.‡ These investigators questioned, perhaps rightly, the ascription of the initial natriuresis to a volume mechanism, since the possibility of dilution of "some essential plasma constituent" or humoral agent was not ruled out. However, during a later phase of the response, water reabsorption, despite vasopressin, falls below that of sodium, suggesting that under these experimental conditions, the former is influenced by factors other than antidiuretic hormone and presumably related to volume.

Localization of Volume Receptors

While some of the aforementioned experiments point to certain sites in the vascular system, neither the exact nature and localization of the receptor structures nor the pathways by which their responses are transmitted have been elucidated. Only the effector organ—the kidney—is known, and that largely by elimination. Except under conditions of profuse perspiration,§ water loss via the skin, lungs, and intestinal tract is fairly constant; electrolyte removal via the skin and in the feces also varies between narrow limits. The very magnitude of the adaptations are such that only the kidneys are capable of sufficient versatility to effect the responses.

The existence of osmoreceptors in the area of distribution of the carotid artery has led investigators to consider the likelihood of similar volume or, as they may function, pressure receptors in the same general area. The effects of recumbency on electrolyte excretion noted by many workers [5,58,78,164] and more extensively explored by Strauss and his colleagues,[182,204,205] further stimulated interest in the cephalic region, although many of the experimental results can be attributed to the venous return and stimuli exerted on the walls of the great veins and right atrium. In fact, the observation that superior vena caval obstruction causes a more pronounced effect than inferior caval obstruction,[61] in that urinary water and electrolyte excretion remain depressed after deflation of the balloon, tends to minimize the importance of volume influences in the head.‖ This finding is compatible with the clinical observation of persistent edema in the superior vena cava syndrome.¶

The nature and function of cephalad receptors was studied extensively by Harrison and his co-workers,[128,129,132-134,141,212] whose findings may be summarized as follows: The decreased sodium excretion on sitting up is again increased by venous neck compression.[128,129] This rise occurs without significant change in cardiac output (measured by electrokymography), urine flow, or glomerular filtration rate and therefore is due to altered renal tubular activity in some way responding to an intracranial receptor regulating extracellular fluid volume. However, neither further lowering of the head nor cervical compression during recumbency causes any further increase in urinary sodium or water excretion.[212]

Conversely, in a sitting, normal subject, moderate bleeding (2.5 ml/kilogram) produces a fall in urinary sodium excretion without change in cardiac output or glomerular filtration rate. Neck compression prevents this decrease which is therefore attributed to a change in intracranial blood and/or extracellular fluid volume. However, severer bleeding (9 ml/kilogram), even in a recumbent subject, causes a marked fall in sodium excretion not averted by neck compression.[133] Since venous congestion of the legs decreases urinary sodium excretion while that of the head increases sodium output, the question of the distribution of extracellular fluid, in contrast to volume, arises. When redistribution occurs without change

‡ The glomerular filtration rate of the dog is more variable than that of man and is therefore more important in maintaining salt and water balance.

§ The composition of sweat may be influenced by volume factors, but this is a relatively unimportant contribution.

‖ Unless by "volume," one refers to flow as well.

¶ Here, the edema is localized to the areas drained by the obstructed channels, is purely mechanical (increased capillary hydrostatic pressure), and is not due to decreased salt and water excretion.

in volume by bandaging the legs in the sitting subject, sodium excretion increases, and after the bandages are removed, it falls. In the recumbent subject, already at a higher intracranial blood volume, the results are variable. These findings, while compatible with the existence of intracranial volume receptors, also support the view that the distribution of fluid, as well as total volume, regulates sodium excretion.

When cervical compression is carried out in patients in congestive failure, unlike in normal subjects no increase in sodium excretion occurs, volume regulation being counteracted by the preexisting intensive sodium retention.[134] In both the sitting and the recumbent positions, cardiac patients retain more ingested sodium and water than do normal subjects, the greater fall in serum electrolyte concentration in the former suggesting that primary water retention occurs. Moreover, cardiac patients fail to exhibit the normal difference in response between the sitting and recumbent positions.[132]

While these results are highly suggestive of the existence of intracranial volume receptors, the possibility of other simultaneously acting influences elsewhere remains. Moreover, Netravisesh [158] was unable to corroborate some of Harrison's findings in that neck compression in sitting subjects did not affect sodium and water excretion. The influence of acute intracranial pressure and volume changes in the dog was studied by Fishman,[64] who found that neither (1) cervical compression, producing a threefold pressure increase in the jugular bulb and a secondary twofold rise in cerebrospinal fluid pressure, (2) cervical compression plus cerebrospinal fluid drainage, causing increased jugular bulb pressure without change or decrease in cerebrospinal fluid pressure and volume, nor (3) intracisternal injection of saline, which increases the cerebrospinal fluid pressure without change in jugular bulb or arterial pressure, produces significant changes in urinary salt or water excretion or renal hemodynamics. In addition, bilateral carotid artery ligation, which promptly reduces the cerebral blood flow, has no effect on salt excretion. The author concluded that his experiments offer no support for the existence of an acutely responding intracranial volume receptor. However, such differences between species whose normal postures differ so strikingly might be anticipated.

Many experimental procedures designed to establish the existence of cephalad volume receptors involve changes in venous return. Furthermore, experiments entailing venous congestion or deviation of part of the plasma result in diminished flow as well as decreased plasma or blood volume, increased sequestrated extracellular fluid volume, and reduced venous return. During the experimental period, there is also a fall in right atrial [151,213] and pulmonary arterial [152] pressures and pulmonary volume. Therefore, receptors sensitive to volume or some related function have been sought in the great veins and lesser circulation.

In 1921, Bazett and Haldane [11] noted the diuresis occasioned by warm baths and subsequently observed that the increased urine flow and associated increased excretion of chloride and urea were independent of the temperature of the bath but required that the entire trunk, not only the limbs, be immersed.[12] Under these circumstances, a large increase in peripheral venous pressure (over 25 cm. of water) was encountered. These authors postulated an increased central venous pressure acting upon pressure receptors in the large veins. At that time, the Bainbridge reflex was known and the contribution of increased venous pressure and distention recently defined.[185] Later, Nonidez found nerve end-organs in the walls of the vena cavae, pulmonary veins, and both auricles resembling those in the carotid sinus which he regarded as pressor receptors.[160] Since then, many experimental and clinical observations involving the reflex effects of pulmonary circulatory obstruction on respiration and circulation have attested to the existence of such receptors.[227]

Drury and co-workers [46] studied the effects of positive pressure breathing in normal subjects and found that at pressures

greater than 20 mm. of Hg above atmospheric kidney function falls sharply, remaining depressed one to two hours after positive-pressure breathing is discontinued. Breathing against somewhat higher pressures produces a decreased cardiac output, with faintness and feeble pulse. The investigators concluded that resistance to blood flow leads to pooling of blood in the extremities, similar to that seen during quiet standing, with hemoconcentration and decreased effective blood volume, and emphasized the disproportionate fall in renal circulation associated with any circulatory impairment.

The converse procedure, namely, negative-pressure breathing, was studied by Sieker, Gauer, and Henry.[72,192] Previously, these investigators had demonstrated that in hemorrhage and subsequent reinfusion the central venous pressure linearly falls and rises with moderate changes in the blood volume, and therefore no compensatory action of the venomotor mechanism occurs.[71,94] Moreover, changes in urine flow parallel those of volume despite minimal changes in mean arterial pressure; in addition, the density of the lungs on x-ray decreases following hemorrhage. Following the suggestions of Schweigk and Schaefer, they postulated the detection of changes in blood volume by nervous stretch receptors in the thoracic viscera. In "sensing" the blood available to the left ventricle and conveying this information to the kidneys, the receptors cause increased blood volume to promote diuresis and decreased volume to lead to oliguria. Working with human subjects and anesthetized dogs, these workers found negative-pressure breathing to produce increased flow of a dilute urine, so that electrolyte excretion, as well as the glomerular filtration rate, remain unchanged. These findings were interpreted as resulting from engorgement of the great veins and lesser circulation secondary to the reduced alveolar and intrathoracic pressure, the congestion, in turn, affecting sensitive receptors It is not improbable that volume receptors would act most effectively in a low pressure, high flow, and high distensibility area, as exemplified by the pulmonary and venous circulation. However, according to Holt,[103] while positive-pressure breathing considerably reduces the cardiac output, negative-pressure breathing produces little change, and therefore little central engorgement is likely to occur. Indeed, Holt's finding of an increased pressure gradient between the peripheral veins and the right atrium in the absence of increased cardiac output implies increased venous resistance to return flow.

Respiratory alkalosis was ruled out as a cause of the diuresis, for while this condition gives rise to increased urine flow, the diuresis is that of an alkaline urine containing considerably increased quantities of sodium and potassium.[85,109] Furthermore, hyperventilation with a gas mixture of 5% to 7% carbon dioxide, which prevents alkalosis, nevertheless gives rise to a water diuresis.[10]

In attempting to localize further the site of the intrathoracic vascular receptors, these investigators[95] produced pulmonary arterial hypertension by the intravenous injection of plastic beads 40 to 100 μ in diameter. The urine flow was not affected in any of six anesthetized dogs. However, on obstruction of either pulmonary artery by ligature or intravascular balloon, a moderate increase in urine flow was recorded in 8 of 11 animals, presumably due to increased flow and engorgement of the unobstructed side. On pulmonary venous occlusion by means of ligature, each of four dogs exhibited definite water diuresis. On the basis of these observations, the sensory receptors were believed to lie in the pulmonary capillaries or veins rather than in the arteries. The effects, therefore, are not necessarily to be equated with those due to increased venous return and right atrial pressure. These results and conclusion are compatible with and provide an explanation for the seemingly paradoxical findings of Drury and co-workers.[46] The latter, it will be recalled, observed a decreased urine flow despite pulmonary engorgement. However, because the ob-

struction was alveolar, the distention was limited to the arterial side.

The afferent pathway for this volume response was studied by interfering with different sensory nerve supplies.[95] Since all of five thoracic sympathectomized dogs responded to negative pressure breathing with the usual diuresis, whereas only one of six dogs whose cervical vagi were blocked by cold or section manifested even a slight diuretic response, the authors concluded that the afferent impulses from intrathoracic stretch receptors responsible for the diuresis travel via the vagi.

The efferent mechanism acting upon the kidney is not established, but the increased urine flow and decreased electrolyte concentration strongly suggest inhibition of posterior pituitary antidiuretic hormone release. In this respect, it is of interest that these authors attribute cold diuresis to peripheral vasoconstriction with consequent filling and engorgement of the pulmonary circulation, while Bader and co-workers[7] reported that experimentally produced cold diuresis is inhibited by quiet standing or walking, or by very minute amounts of vasopressin.

Despite intensive study of the cephalad region, the great veins, and the pulmonary circulation, little is known of the nature of the volume receptors. From the experimental results with arteriovenous fistulae, the suggestion has been made that receptors in the arterial system may apprise the body of the fullness or distention of the arterial bed and therefore of volume.# As such, it is important to bear in mind that circulatory flow may act in such a way as to be interpreted as volume. This will be further discussed below. The effects of cellular dehydration and overhydration, resulting in decreased and increased renal tubular sodium reabsorption, respectively, suggest that the cell membranes may contain receptors sensitive to the fullness or tension of these structures. In any event, the so-called volume receptors appear to be essentially pressure-sensitive end-organs, pressure being often a function of volume and, at times, of flow.

If these receptors, responding to fullness, distention, or pressure, are postulated to lie proximal to the arterioles, one may be tempted to wonder what happens to them in hypertensive disease.

Fluid Intake or Thirst

Since the kidneys are virtually the only organ capable of varying fluid and electrolyte excretion, renal responses have been exclusively employed to measure the volume regulating capacity of the body. However, in fluid intake or thirst, an even more basic regulatory mechanism exists in that it provides the water upon which other responses act. The complex effects of water, which lowers osmolarity, increases volume, and migrates rapidly intracellularly throughout the body, have already been mentioned.

The sensation of thirst provides very fine control of the body fluid content. The origin or cause of the sensation, in terms of general and local factors, are still a matter of controversy. Proponents of the former position point to Claude Bernard's and later experiments indicating that the thirst of esophagotomized or gastric fistula dogs is not relieved by drinking. Cannon, representing the opposite viewpoint, advanced the idea that lack of water diminishes salivary flow, dries the mucosae, and gives rise locally to thirst sensations. Experiments designed to test these hypotheses, involving pharmacologic stimulation and depression of the salivary glands, surgical extirpation, and other approaches, have led to conflicting results and arguments too extensive for present review.

The most typical and common thirst promoting stimulus is water loss or deprivation (see above). Since the resultant increased osmotic pressure of the blood was established early, the thirst was attributed simply to hypertonicity of the body fluids. The well-known appearance of thirst following the infusion of hypertonic solutions of salt[100] or other substances supports this hypothesis. However, Gilman[74] fed dogs 20% sodium chloride or 40% urea, both of which produce about the same increase in serum osmotic pressure. It will be recalled that

urea, unlike sodium chloride, enters cells freely. In keeping with this fact, Gilman observed that the plasma protein concentration, as reflected in the specific gravity, fell in the salt-fed animals whose subsequent spontaneous water intake was much higher. He concluded, therefore, that salt draws water from the cells into the extracellular fluid and that thirst is due not to increased osmotic pressure of the body fluids per se, but to cellular dehydration. The greater thirst following sugar than equivalent amounts of salt solutions [99,101,203] supports this belief.

In support of his thesis, Gilman pointed out that dogs subjected to Darrow-Yannet peritoneal dialysis,[42,43] dehydrated in terms of salt loss, but whose cells are overhydrated, do not drink much shortly after the dialysis, that is, tend to maintain tonicity at the expense of fluid volume. Moreover, Nadal and co-workers [156] reported that their salt-depleted patients experience no thirst and even exhibit an aversion to water. While Gilman's interpretation with regard to the importance of cellular dehydration was readily accepted, the latter point aroused considerable controversy and resistance. McCance [145] at about the same time reported that his salt-depleted dogs were thirsty despite their hypotonicity, and their diuretic responses to water ingestion were impaired, both characteristics tending to maintain volume rather than tonicity. His salt-depleted human subjects also drank freely, an observation in keeping with the continued drinking of profusely perspiring coal miners incident to the development of heat exhaustion or miners' cramps. Since the salt-depletion procedures require several days whereas the salt loss of peritoneal dialysis is completed in several hours, the rate of salt loss may be crucial in that following acute loss tonicity is protected whereas volume regulation is slower to be brought into play.

These apparently discrepant results were resolved by Cizek and Huang and their colleagues,[32,33] who found that dogs depleted of salt by osmotic diuresis exhibit a gradual increase in thirst despite cellular hydration,* although their water diuresis is impaired. Furthermore, dogs subjected to peritoneal dialysis and followed longer than the 24- to 36-hour period of observation of Darrow and Yannet, thereby given opportunity to recover from the traumatic effects of the procedure, demonstrated considerable thirst and polyuria. Apparently, the early failure to drink is a result of the shock state and lassitude following the experimental procedure, for after this interval, increased intake and water diuresis occur despite the low plasma volume. Evidently, in the absence of both hypertonicity and cellular quite variable among different animals.[101] dehydration, thirst sensation is stimulated in The amount ingested tends to be the same what appears to be an attempt to maintain fluid concentration back to isotonicity, but is volume. The body water content is maintained under these circumstances, not by renal retention, but by stimuli leading to increased intake.

However, that the data are not one-sided, but represent the interplay of several factors, is obvious from the results of Holmes and Gregersen,[100] who found that the thirst and decreased salivary flow, occasioned by not encountered following isotonic saline hypertonic saline despite significant increase in plasma and extracellular fluid volume, is which also increases fluid volume, but without the associated intracellular water loss.

The mechanism of thirst is further complicated by the timing of fluid ingestion and the factors leading to satiation. In contrast to Gilman's original thesis, the amount of water ingested by dogs following the administration of hypertonic saline is not simply that necessary to correct the extracellular whether given promptly or delayed several hours, by which time the animal has compensated by excreting a considerable portion of the salt. Moreover, thirst is satiated long before the water is absorbed or prior to any dilution of the plasma, especially in more rapidly drinking animals, and is in-

* Manifested by constant weight and decreased plasma volume.

fluenced by a number of only partly understood factors.[2,101,102]

The association of thirst with diminished fluid volume and apparently normal tonicity is encountered frequently in experiments involving isotonic fluid loss or deviation. In addition to the renal changes, thirst is a prominent feature of the dehydration reaction.[166,168] The antidiuresis of quiet standing is accompanied by thirst.[58] The extreme thirst following hemorrhage or the fluid loss of surgery, severe injuries, and shock states is a matter of common knowledge. In addition to sweat water loss in these conditions, it is conceivable that disproportionately intensive renal tubular reabsorption of sodium may result in sufficient hypertonicity to draw water from the cells. Because the latter represent a large and available reservoir from which water can migrate rapidly, the extracellular hyperosmolarity may not be measurable. Nevertheless, the cellular dehydration may be adequate to stimulate thirst. Data obtained by Wolf [234] indicate that in man the "thirst threshold" is reached following a calculated relative decrease in cell water of slightly over 1%.

Perhaps the most striking examples of the importance of thirst in volume regulation are encountered in clinical hyponatremic states of diverse origin. The very existence of sustained hyponatremia implies a sacrifice of tonicity in the interests of greater volume, for in these patients the ingestion of water is greater than that indicated by fluid tonicity.[168] There is, however, ample evidence from observation of cardiac and cirrhotic patients that any attempt to increase their fluid osmolarity gives rise, even at subnormal levels, to extremely intense thirst. In these patients too, the further decrease in effective circulating volume or, more specifically, the further aggravation of their impaired circulatory status associated with additional edema formation, paracentesis and reaccumulation of ascites, and other circulatory sequestration, leads to increased thirst.[157,168]

Since thirst sensation is finely regulated, not only in its onset, but in its prompt satiation, spontaneous overingestion of water is very rare. Anuric animals are not, as a rule, edematous because they drink just enough to maintain fluid volume and effective osmotic pressure. Anuric or extremely oliguric patients are sometimes less fortunate, in that the edema occasionally encountered is iatrogenic in origin, consequent to attempts to initiate urine flow by forcing the intake of water. However, thirst often persists in edematous patients—many of whom are cardiacs—who drink because the receptors indicate a need for fluid volume. In these cases, the initiating stimulus, certainly not decreased extracellular fluid volume or necessarily cellular dehydration, may reside in the closely related parameter, circulatory flow.

While thirst is finely regulated and appears during very slight changes in body fluid content, it can exist only in subjects whose sensoria are sufficiently clear to receive and interpret the responsible afferent impulses. Recently, interest has been focused on the marked and dangerous hypernatremia of patients with impaired states of consciousness who either are too depressed to be aware of thirst or are unable to communicate their desire for water.[217] In terms of fluid balance, such patients are in the same position as persons lost in the desert or at sea—or experimental subjects deprived of water. Hypernatremia associated with central nervous system disease, but not necessarily with disturbed states of consciousness, has also been described.[3,4,38,217] The hypertonicity of these patients is not simply an impaired thirst response, but appears to be due to an altered setting of the mechanism responsible for regulating body fluid osmolarity. Experimental damage to nuclei of the hypothalamus has resulted in hypernatremia or "chronic hypothalamic hypodipsia."[130,201]

Hydration and Prehydration

In addition to regulating fluid intake via thirst, volume factors play an important

role in maintaining normal fluid content by presetting or conditioning the responses to additional fluid intake. Experiments in which the intake of water following hypertonic saline resulted in water diuresis while the extracellular fluid was hypertonic have been referred to.[8,17] The more general phenomenon, namely, the greater urinary excretion of sodium following salt administration to subjects previously given salt freely than in those denied access to salt, has been well established.[215] The observation that the osmotic diuresis following infusion of 10% urea, which has little effect on salt excretion in normally hydrated subjects, actually reduces salt output in hydropenic persons, reflects another manifestation of this activity. Similarly, dogs maintained on a low salt diet prior to mannitol osmotic diuresis, exhibit less natriuresis than those on a previously high sodium intake.[193]

The influence of conditioning or prehydration was studied more extensively by Ladd,[116,117] who gave water prior to infusing isotonic salt (3000 ml.). The latter was followed by a dilute urine ("water") diuresis which was maximal when the water ingestion preceded the salt by 8 to 13 hours. The fact that this response was inhibited by vasopressin or hypertonic saline suggests that it is dependent upon posterior pituitary antidiuretic hormone inhibition. Birchard and Strauss[18,19] found that the ingestion of a liter of isotonic saline results in no appreciable diuresis. If the normal (seated) subject is given this dose during subsidence of diuresis, a slight and transient diuresis occurs. But the ingestion of saline by a normally hydrated subject given excessive salt during the previous day is followed by a prompt diuresis of dilute urine. Because this latter effect does not occur in hydropenic subjects, these workers also concluded that antidiuretic hormone inhibition underlies the response.

Many of the experimental results on prehydration appear to implicate the tubular sodium load. As shown, the sustenance of water diuresis requires adequate solute excretion and is most influenced by those factors which determine solute loss.[181,182] However, the absence of measurably significant changes in glomerular filtration rate or plasma sodium concentration render this point insusceptible to proof.† During Ladd's studies, involving prehydration with water, it would seem that within eight hours, or prior to the time of maximal response, its effects should have been dissipated.

Mechanisms Underlying Volume Regulation

The kidneys function as a final common pathway through which various influences, i. e., electrolyte concentration, total osmolarity, previous state of hydration, circulatory status, etc., are mediated, and, aside from intake and slight variation in sweat loss, govern and control the fluid volume. In addition to distant influences, hormonal and possibly neurogenic, intrarenal mechanisms affect electrolyte and water excretion. While it is difficult experimentally to seperate hormonal effects carried in the renal blood supply from local influences, evidence for the existence of the latter has accumulated. The unilateral effects of intrarenal arterial injections and renal venous compression have been mentioned[22,77,188]; ureteral obstruction produces unilateral functional changes. The increased tubular electrolyte reabsorption with decreased renal circulation or filtration of many orgins has been well documented. In perfusion experiments during which the perfusion pressure was varied over a wide range, the more extreme levels were associated with alterations in function.[189,191] In view of the diverse functions regulated by the kidney by means of intrarenal enzymatic systems, some of which are known to involve electrolyte output, it is not surprising that such local control exists.

One additional body system—the circulatory—exerts an important control of fluid volume, and when it is impaired, severe manifestations of derangement of fluid volume and distribution occur. The effects of diminished flow, or shock, and of local ac-

† Footnote § under "Isosmotic Fluid Loss and Deviation."

cumulation of fluid in otherwise normal organisms has been extensively studied. The physiologically impaired "volume" implied is counteracted by a variety of mechanisms—vasoconstriction, especially in the kidneys and skin, redistribution, withdrawal of blood or fluid from body reservoirs—all tending to maintain some degree of adequate flow.[26,45,214] Conversely, the induction of increased volume, a rarely spontaneously encountered phenomenon, is followed by equally efficient methods of removal in the normal subject. However, chronic vasopressin administration experiments indicate that cardiac patients, whose vascular systems cannot cope with the increased load, do not respond in normal fashion.[223] In the presence of inadequate circulatory function, an abnormally high fluid volume is frequently interpreted as an inadequate one and is associated with the activation of factors tending further to increase fluid retention. The implications of this situation will be further discussed.

While the afferent pathways, with the exception of the vagal fibers from the lesser circulation (see above), through which volume effects are exerted, are unknown, the control of renal water and salt excretion appears to be regulated by the posterior pituitary and adrenal glands, respectively. Numerous experiments attest to the altered responses of the former, independent of and frequently in the face of concentration changes. The abnormal responses of diabetes insipidus patients[208] and the effects of vasopressin during abnormal experimental conditions also point to this influence of the posterior pituitary.

Relative changes in urinary sodium concentration and excretion compared to water output may aid in the evaluation of antidiuretic hormone activity.[152,170] Unfortunately, antidiuretic hormone assay remains a difficult method beset with errors, so that direct evidence of its presence is difficult to obtain. Nevertheless, it has been found in increased quantities in Darrow-Yannet salt-depleted, hyponatremic animals[124] and, clinically, in congestive failure[15] and other fluid-retaining states. Moreover, Winter and co-workers[232] demonstrated that posterior pituitary antidiuretic hormone is necessary for the production of a concentrated urine during hyponatremia following salt depletion. Their adrenalectomized cats were hyponatremic, but diabetes insipidus cats subjected to adrenalectomy failed to develop the characteristic low plasma sodium levels until vasopressin, in doses sufficient to control the polyuria, was administered. These investigators concluded that the antidiuretic response of a adrenal insufficiency requires an intact posterior pituitary. This coincided with the results of Martin and co-workers,[144] who found, in salt-depleted and adrenalectomized cats, increased antidiuretic activity proportional to the fall in serum sodium concentration.

Because instrinsic renal and other factors affect sodium loss, the role of the adrenal cortex in transmitting volume effects regulating sodium excretion is less clearly defined than is that of the posterior pituitary with regard to water output. The reaction to stress, in addition to other widespread metabolic effects, plays an important part in maintaining normal fluid volume and composition. Postoperative salt and water retention[26,76,230] provides an example of this adaptive process, for even when adequate water is not provided, salt is retained and tonicity is sacrificed in an attempt to preserve volume. The increased potassium excretion during such fluid loss or experimental fluid deprivation has been regarded as a mechanism to facilitate withdrawal of cellular water, as Borst[26] put it, "for the purpose of restoring the normal filling of the arterial system by way of an augmentation of the total extracellular fluid, and therefore of the blood dilution." The more generic "dehydration reaction"[166,167] assumes that any diminution in effective blood volume stimulates production of the salt-retaining hormone of the adrenal cortex, with sodium and, consequent, water retention. The abnormal responses of adrenalectomized animals, not only to salt depletion,

but to salt or water loading,[115,180] is evidence of impaired volume regulation. However, the importance of the contribution of the adrenal cortex remains a matter of controversy, for while the antisaluresis encountered during quiet standing is reduced in adrenal insufficiency,[58] neither corticotropin, cortisone, nor desoxycorticosterone affected salt excretion in the tilting experiments of Holland,[98] who concluded, therefore, that the diminished output on tilting is not due to adrenal activity. Moreover, the decreased sodium excretion following hypertonic albumin administration is encountered in adrenal insufficiency and therefore is also otherwise mediated. The large variability of tubular sodium reabsorption observed by Rosenbaum and co-workers [183] in Addisonian patients on constant steroid dosage tends to minimize the role of the adrenals. However, this flexibility of response, while not dependent upon changing adrenal steroid function, is not obtained by desoxycorticosterone alone, but requires basic corticoid activity.

The difficulties in evaluating adrenal cortical influences are enhanced by the number of chemicals elaborated, by their various various synergistic and antagonistic effects, and by the multiplicity of effects of single steroids which, particularly at varying dosage, may counteract one another.[119] Just as vasopressin does not produce clinical edema and is counteracted by secondary volume effects, the continued administration of desoxycorticosterone to the normal subject does not result in persistent, progressive sodium retention, but in secondarily increased urinary flow and sodium excretion,[168,175] and in dogs produces a diabetes-insipidus-like syndrome.[154,174] Apparently, on prolonged desoxycorticosterone treatment, the sodium and water retention result in extracellular hypervolemia.[70] Natriuresis follows, and by osmotic withdrawal and/or antidiuretic hormone inhibition, increases the water output. As in the case of vasopressin, the secondary natriuresis and diuresis is associated with an increased glomerular filtration rate. Is is of interest that the recently described clinical syndrome, primary aldosteronism,[36] involving excessive production of salt-retaining adrenal cortical hormone (see below), includes polydipsia and polyuria but not edema.

Unlike cortisone, which produces a prompt rise in the renal hemodynamics and sodium excretion of adrenally insufficient subjects, independent of plasma volume, desoxycorticosterone has no acute effect on glomerular filtration, but produces a delayed rise when given in adequate doses.[34,69,131] That this rise is related to volume regulation is clear from the observation that it is entirely prevented by low sodium intake. Of additional significance is the fact that during the secondary diuresis sodium excretion varies directly with the glomerular filtration rate.[69]

The effects of the corticoids are equally complex and depend upon the organism as well as the drug. The sodium-retaining activity of these compounds, already less than that of desoxycorticosterone, is acutely counteracted by their tendency to increase glomerular filtration, particularly in the hypoadrenal subject, the final result depending upon the relative influence of these conflicting actions. Thus, hydrocortisone, in either low or high dosage, produces a prompt and striking increase in glomerular filtration and sodium excretion. However, on the high dosage, gradually increasing tubular sodium reabsorption leads to a fall in sodium output to the control levels.[119] The over-all effect at any time is a function of the relative changes in sodium filtration (GFR) and its tubular reabsorption. Cortisone, as a rule, in adrenal cortical insufficiency and adrenalectomized animals has little effect or may decrease sodium loss, but restores water diuresis and thereby corrects the hyponatremia and hypochloremia.[30,178]

Aldosterone

The effects of desoxycorticosterone have long been attributed to a naturally produced salt-retaining hormone, not further identi-

fied, whose principal function is to maintain the volume of the body fluids. Gordon and co-workers,[81] using a sensitive biological assay, and Deming and Luetscher[44] found high urinary titers of a sodium-retaining factor, believed to be a steroid of adrenal cortical origin, in patients with fluid retention and edema secondary to congestive failure, toxemia of pregnancy, hepatic cirrhosis, and renal disease. Some correlation between the titers and degree of fluid retention was observed. Shortly afterward, the isolation and crystallization of electrocortin, or aldosterone,[195] stimulated continued interest in the sodium-retaining behavior of the adrenal cortex.

Employing paper chromatography, Luetscher and Johnson[138] found a sodium-retaining fraction in the urine of edematous patients which, while presumably of adrenal cortical origin, did not correspond to any earlier known adrenal cortical hormone but resembled aldosterone; moreover, no other fraction contained significant sodium-retaining activity. In a series of subsequent studies, Luetscher and his colleagues[6,139] observed that in normal subjects during unrestricted sodium intake, sodium-retaining activity was extremely difficult to demonstrate, requiring large amounts of urine. After adrenalectomy, however, this normal amount of activity disappeared completely.[136] Dietary sodium restriction to 15 mEq. daily led to a fivefold increase of excretion of sodium-retaining activity; this figure remained elevated until normal sodium intake was restored. When activity was related to sodium restriction, it was found to bear an inverse, linear relation to sodium excretion, especially at outputs less than 50 mEq/day.[139] The activity produced by salt restriction possessed chromatographic mobility identical with that of the sodium-retaining corticoid from edematous patients; the latter was later identified as aldosterone.[140] Increased urinary excretion of sodium-retaining activity was not accompanied by associated changes in the output of 17-ketosteroid or 17-hydroxysteroid. Therefore, it was concluded, sodium restriction stimulates production of aldosterone.

The increased sodium-retaining activity of clinical edematous states, i. e., congestive failure, cirrhosis, nephrotic syndrome, was found to lie in the same chromatographic fraction of each extract and to correspond to that seen on salt restriction or other diminished extracellular fluid volume. Aldosterone production, therefore, represents a measure for conserving sodium independent of the state of hydration of the body per se and may be related to circulatory efficacy. So fundamental is this mechanism that, unlike the release of other adrenal corticoids, it is relatively independent of corticotropin control.[131,137] The latter was established by direct administration of corticotropin and by the observation that adrenalectomized patients maintained on cortisone, and eucorticoid, develop salt-depletion syndrome on sodium intakes less than 20 mEq. daily, whereas hypophysectomized patients with intact adrenals maintain normal sodium balance on less than 10 mEq. of sodium per day.[142] Its excretion is not significantly affected by clinical conditions involving changes in urinary 17-ketosteroid and 17-hydroxycorticoid output,[137] and cortisone does not decrease the aldosterone excretion of sodium-depleted subjects. Conversely, the increased aldosterone output associated with low sodium intake is not accompanied by changes in excretion of other steroids.[137] The high specificity of aldosterone activity is reflected in its inability, even in what is now considered high dosage, to overcome the adrenal insufficiency of an adrenalectomized human whose cortisone was withdrawn.[142]

The regulation of aldosterone production was studied by Liddle and co-workers,[131] who demonstrated the importance of volume factors behind its control. Sodium restriction consistently increased the excretion of aldosterone; potassium administration produced the same effect only in subjects in whom it also caused sodium loss. Thus it may be inferred that of the sodium-retaining and kaliuretic effects of aldosterone, the primary one is to increase sodium reab-

sorption, the increased potassium excretion resulting from greater distal tubular ionic exchange between the two cations. However, in sodium-depleted, normal subjects whose aldosterone excretion was high, the administration of vasopressin and adequate water which, as described, increases sodium excretion despite the hyponatremia, brought about decreased aldosterone excretion. Therefore, volume changes, rather than the concentration or body content of sodium, determine aldosterone release and excretion, which underlies the biphasic response to vasopressin noted by Leaf [122] and Weston.[224] This was confirmed by Beck and co-workers,[14] who studied two normal subjects on high salt intake. Following natriuresis and discontinuance of vasopressin, aldosterone excretion promptly rose to very high levels. When, however, the vasopressin was continued after sodium loss, with continued water retention, aldosterone excretion rose relatively little. While the data are limited, they suggest that loss of water or volume, rather than sodium per se, stimulates aldosterone release. In view, though, of the fact that intravenous albumin, which expands the vascular compartment at the expense of the extravascular space, does not decrease aldosterone excretion,[131] the controlling fluid volume is not simply that of plasma or blood.

In this respect, Prunty and co-workers [173] showed, in an Addisonian patient, that aldosterone produces a transfer of water from the intracellular to the extracellular fluid space. However, in adrenalectomized animals,[87] it is not as actively water retentive as desoxycorticosterone. This may be related to its greater tendency to increase renal hemodynamics,[176] thereby counteracting the renal tubular effect. Small doses which produce sodium retention may be insufficient to increase the low glomerular filtration rate of adrenalectomized cats.[184]

Clinically, other than in primary aldosteronism, high aldosterone excretion is encountered chiefly in those conditions involving fluid retention and edema, and designated as secondary aldosteronism. Very high urinary levels have also been found in congenital adrenal hyperplasia and in salt-losing nephritis.[137] The latter, stimulated by sodium and volume depletion, represents a vain body attempt to prevent sodium loss, futile because of the inability of the damaged renal tubules to respond to the hormone. Edema, however, is not itself a cause of increased aldosterone production, for when edematous patients are given isotonic saline solution, aldosterone excretion is decreased.[131] This finding further emphasizes the primacy of volume factors—in the broadest sense of the word—in aldosterone production.

Volume Regulation and Hyponatremia

Hyponatremia—its pathogenesis, nature, and treatment—has been extensively reviewed [40,54,125,215] and requires no further elaboration here. The hyponatremia described by Peters and his colleagues [169] may not be essentially different, except in rate of development, from that of any salt depletion. However, since it is of slow onset, the body appears able to adjust its "normal" sodium level to the new circumstance, and so the condition is relatively benign and asymptomatic.

The hyponatremia secondary to sodium loss, as in Addison's disease, has been experimentally reproduced in the experiments of McCance and others. The decreased sodium level has been attributed to an attempt to maintain fluid volume at the expense of normal tonicity by the continued release of endogenous antidiuretic hormone, a conclusion supported by the experiments of Winter and co-workers,[232] whose diabetes insipidus cats failed to become hyponatremic following salt depletion.

Most clinical hyponatremia—that seen during edematous states—follows a quite different pattern from the above and from others experimentally produced. In the latter, it is apparent that those body mechanisms for maintaining fluid volume, insofar as they lead to withdrawal of intracellular water, also dilute the extracellular fluid. However, the extracellular fluid volume and that of other compartments of

many hyponatremic conditions is either normal or considerably increased. Certainly, there is no inadequacy of volume to be counteracted. Moreover, while a low sodium intake characterizes therapy, and may conceivably play a small role in the tendency to develop hyponatremia, most patients are in normal sodium balance and may have a supernormal body sodium content. Consequently, the hyponatremia must be more intimately associated with the migration of water than with that of sodium.

The development of congestive failure is associated with both salt and water retention. Since recovery usually involves greater loss of water than sodium,[153] it is highly probable that excessive water retention occurs during decompensation. This is borne out by the repeated,[66,153,198] but not universal,[106] observation that the serum sodium level of cardiacs in failure is significantly lower than that of normal subpects.‡ However, the reduced extracellular sodium concentration may be due to migration of sodium into cells, as suggested by Iseri,[106] for as Farber and Soberman[62] showed, in cardiac patients, unlike in other edematous patients, the ratio of exchangeable sodium to total body water is increased.

The aggravation of preexisting failure is often associated with further falls in serum sodium concentration. This has been repeatedly observed in terminal failure and on intensification of failure by concomitant infection, digitalis withdrawal, or digitalis toxicity.[222] In these conditions, in which sodium balance is unaffected, urine volume falls with decompensation and rises coincident with recovery. A similar hyponatremia due to water retention is encountered in cardiac patients undergoing surgery (mitral valvulotomy).[76,230] The water retention of circulatory impairment appears to be a mechanism for maintaining volume when that parameter may be normal or even increased, but when a differential function, namely, flow, is inadequate. Just as the rising oncotic pressure following albumin administration is interpreted by the body as a manifestation of plasma fluid loss, with consequent sodium retention, in a similar manner the decreased circulatory flow is sensed as a diminished volume and is counteracted by further water retention.

The observations of McDowall and Zayat[150] are of interest with regard to the hyponatremia of severe congestive failure. They found that isolated rat cardiac muscle, depressed by anoxia, is improved by reducing the sodium concentration of its medium. This enables the muscle to contract more forcibly at higher rates and therefore do more work. The clinical implications are obvious.

The hyponatremia of the cirrhotic patient in some respects resembles that of the cardiac, involving low sodium intake, increased volume, and diversion of fluid from the active circulation. The latter is particularly significant in the hyponatremia following abdominal paracentesis.[157] After removal of ascitic fluid, there is considerable fluid redistribution as manifested by subsidence of edema without decrease in body weight[68] and accumulation of more ascites than can be accounted for by weight gain.[143] This redistribution and further loss from the actively circulating mass stimulates volume mechanisms resulting in increased retention of water and further hyponatremia. The rapid loss of salt and water during mercurial diuresis often acts in a similar fashion and may be followed by increased water retention and hyponatremia.§

‡ Opponents of this viewpoint[106] attribute this finding to the lower sodium intake and previous therapy of the cardiac patients. While this may play a part, it is unlikely that normal subjects on equivalent sodium restriction would develop such low serum sodium concentrations. Moreover, any tendency of the sodium concentration to fall during dietary sodium restriction reflects a volume adjustment beyond maintenance of osmotic pressure.

§ Subsidence of mercurial diuresis, in fact, may be associated with, and possibly due to, increased release of aldosterone[47] and/or other active compensating mechanisms.[68]

Summary

A constancy of body fluid volume in addition to, and, at times, independent of tonicity, is actively maintained. The mechanisms responsible appear to regulate, too, the distribution of the fluid. Because adaptation to change in fluid volume is relatively slow compared to other responses, mediation is probably accomplished by humoral or hormonal, rather than neurogenic, routes. In most studies, the kidneys, most responsible for the body's fluid composition, have been much more sensitive to hormonal stimulation than to attempts to modify their nerve supply.

Of the fluid spaces, the extravascular, extracellular fluid compartment appears to be most instrumental in the regulation of volume control. Thus, under experimental increase of the plasma volume (concentrated human albumin) or the intracellular fluid volume (peritoneal dialysis) at the expense or contraction of the extracellular fluid, the body reacts by retaining salt and water. Lying functionally between the plasma and intracellular fluid and in equilibrium with both surrounding compartments, the interstitial fluid determines their composition and size by as yet only partly understood effects. In part, the relative impermeability of the capillary membrane to plasma protein is responsible for the ratio of the size of the interstitial to the plasma compartments. Since at constant plasma oncotic pressure the interstitial fluid and plasma volumes move in parallel fashion, changes in the former may be exerted anywhere in the vascular tree. When, however, the ratio is disturbed, as in hypoproteinemic edema of any cause, with consequent increase in interstitial fluid volume and decrease in plasma volume, the body reacts to overcome the plasma abnormality by further fluid retention. This correction of plasma volume at the necessary expense of further abnormality of the interstitial fluid is an illustration of the supersedence of maintenance of adequate circulation over volume.

While specific volume receptors have not been identified, their influence on the kidneys is exerted primarily via the posterior pituitary and the adrenal cortex. The former largely controls the excretion of water, the latter, of sodium. In addition, intrinsic mechanisms within the kidneys, affected chiefly by hemodynamic factors, exert additional control of electrolyte output. The dominance of the posterior pituitary and adrenal on water and salt output, respectively, is considerable, but rendered quite complex by the influence of their secretions on each other. The marked hypophyseal control of water excretion is reflected in the inability of subjects with diabetes insipidus, subjected to procedures involving fluid loss, to protect their water content. However, even this conspicuous regulation is not absolute. Since urine flow is a function of tubular load as well as antidiuretic hormone activity, reduction of the former secondary to diminution of fluid volume minimizes the loss of water even in diabetes insipidus. Similarly, the control exerted by the adrenal cortex is modified by extrinsic influences. The decreased salt and water excretion following concentrated albumin infusion occurs in adrenal insufficiency. Evidently, the adrenal cortex is by-passed by a direct effect on the renal tubules. Moreover, the latter demonstrate considerable variability of sodium reabsorption in Addisonian patients on constant cortisone dosage. Lastly, the sustained administration of salt-retaining steroids is counteracted by the increased volume and consequent increase in sodium and water excretion. Thus, in primary aldosteronism, polyuria and polydipsia occur, but not edema. It is reasonable to suppose, therefore, that the volume stimulus or fluid retention of secondary aldosteronism represents a mistaken stimulus in that an impaired circulatory flow is "sensed" by the receptors as an inadequate volume. Evolutionally, the more primitive survival threat is fluid loss resulting in contraction of volume and diminution of flow. The latter may itself therefore be an adequate stimulus for the maintenance of volume. The onus for the apparent senselessness of the renal tubules of the cardiac, cirrhotic, or nephrotic

in continuing to reabsorb sodium in the presence of superfluous amounts may be shifted one step back to these volume mechanisms which, via aldosterone, continue to "drive" the tubules.

Whatever evidence is available indicates that the receptors may be multiple in location and act on either salt or water excretion. The experimental immobilization of fluid by venous congestion decreases the plasma volume without change or localized increase in interstitial fluid volume. At the same time, the venous return is reduced. The resultant retention of salt and water appears therefore to be a response to the change in plasma volume or flow, and based on vascular receptors. Such end-organs, which could respond to volume or flow, have been described in the great veins entering the heart. On increased venous return (exercise, rapid saline infusions), these accelerate cardiac action via the Bainbridge reflex and on reduced flow and venous filling produce peripheral vasoconstriction (vagopressor reflex) and reduce salt and water excretion in an attempt to maintain effective volume or flow. However, in the presence of an arteriovenous fistula or other high output failure involving decreased peripheral resistance and greater venous distention and flow, the expected response characteristic of increased volume, namely, increased salt and water output, does not occur. Similarly, in congestive failure, in which the increased venous pressure is, however, combined with reduced flow, the greater plasma volume is associated with increased retention of salt and water. The responses of these volume receptors in failure are qualitatively different from that in the normal state and depend not only upon volume or even flow as such, but upon flow as related to metabolic demands. Therefore, the ability of the heart to meet its obligations may determine the normality of response.

Negative-pressure breathing experiments have demonstrated the existence of similar receptors in the pulmonary veins, stimulation of which by distention inhibits the posterior pituitary. An increased pulmonary volume or congestion is thereby overcome by increased water excretion and the left side of the heart protected against overdistention. While, to the best of my knowledge, this experiment has not been attempted in patients in congestive failure, it is highly unlikely that they would respond in normal manner. Many patients with predominantly left-sided heart disease and failure have pulmonary congestion without correspondingly increased water excretion. An analogous vicious cycle obtains as in the great veins and right heart. While the body may be protected by receptors tending to prevent undue loads, and while moderate increases in volume or vascular distention may represent a well-governed mechanism to maintain or increase flow, the ability to respond or adequacy of the effector organ, the heart, remains a *sine qua non*.

Increased local venous or capillary pressure has also been postulated to stimulate cephalad or intracranial volume or baroreceptors similar to osmoreceptors. However, if so, the decreased salt and water excretion of superior vena caval obstruction or right-sided congestive failure with increased venous pressure is paradoxical, unless, again, the inability of the heart to compensate is assumed.

The salt and water retention, a response to contracted volume, following opening of an arteriovenous fistula and venous engorgement, suggested to some workers the presence of vascular receptors, presumably in the arterioles and capillaries. This site could account for the responses to plasma hypovolemia or shock, the inadequate filling of these vessels leading to arteriolar constriction in an attempt to maintain vessel fullness, not unlike the response associated with decreased venous return. Such receptors might also translate inadequate cardiac output or flow into insufficient volume and bring about the fluid retention of congestive failure. Even high output failure, in which the open arterioles responsible for the decreased peripheral resistance and the in-

creased venous volume cause lower arteriolar hydrostatic pressure proximally, would be sensed as a decreased volume. However, vascular receptors capable of such response would not produce the observed response to hypertonic albumin infusion, unless counteracted by more powerful influences. Moreover, they have not as yet been anatomically defined.

The existence of cellular structures or volume receptors analogous to osmoreceptors has been postulated, the supposition being that their cell membranes, separating intra- and extracellular fluid, may be stimulated by the migration of fluid and/or the differences in tension thereby produced on the membrane. Cellular overhydration favors sodium retention, while cellular dehydration predisposes to increased sodium excretion. Since the former contracts and the latter augments extracellular fluid volume, the principal function of these receptors would involve protection of the extracellular compartment.

The greatest discrepancies in volume regulation are observed in clinical states involving fluid retention. As tonicity regulation gives way to that of volume under certain circumstances, in like manner, volume control yields to the greater threat inherent in circulatory failure. To the extent that an increase above normal fluid volume, by improved vascular filling, increases circulatory efficiency, the mechanism tends to be protective. When, however, a diseased circulatory system cannot be whipped into more effective action, the increased volume becomes a progressively greater burden—literally an "Old Man of the Sea."[207]

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REFERENCES

1. Adolph, E. F.: J. Physiol. 55:114, 1921.
2. Adolph, E. F.: Am. J. Physiol. 161:374, 1950.
3. Allott, E. N.: Lancet 1:1035, 1939.
4. Anthonisen, P.; Hilden, T., and Thomsen, A. C.: Acta med. scandinav. 150:355, 1954.
5. Asmussen, E.; Christensen, E. H., and Nielsen, M.: Surgery 8:604, 1940.
6. Axelrad, B. J., and Luetscher, J. A., Jr.: J. Clin. Invest. 33:916, 1954.
7. Bader, R. A.; Eliot, J. W., and Bass, D. E.: Fed. Proc. 8:7, 1949.
8. Baird, M. M., and Haldane, J. B. S.: J. Physiol. 56:259, 1922.
9. Baldes, E. J., and Smirk, F. H.: J. Physiol. 82:62, 1934.
10. Barbour, A.; Bull, G. M.; Evans, B. M.; Hughes Jones, N. C., and Logothetopoulos, J.: Clin. Sc. 12:1, 1953.
11. Bazett, H. C., and Haldane, J. B. S.: J. Physiol. 55:4, 1921.
12. Bazett, H. C.; Thurlow, S.; Crowell, C., and Stewart, W.: Am. J. Physiol. 70:430, 1924.
13. Beaser, S. B.: Am. J. M. Sc. 213:441, 1947.
14. Beck, J. C.; Dyrenfurth, I.; Giroud, C., and Venning, E.: A. M. A. Arch. Int. Med. 96: 463, 1955.
15. Bercu, B. A.; Rokaw, S. N., and Massie, E.: Circulation 2:409, 1950.
16. Berne, R. M., and Levy, M. N.: J. Clin. Invest. 29:444, 1950.
17. Birchard, W. H.; Rosenbaum, J. D., and Strauss, M. B.: J. Appl. Physiol. 6:22, 1953.
18. Birchard, W. H., and Strauss, M. B.: J. Clin. Invest. 31:617, 1952.
19. Birchard, W. H., and Strauss, M. B.: J. Clin. Invest. 32:807, 1953.
20. Black, D. A. K.; McCance, R. A., and Young, W. F.: J. Physiol. 102:406, 1944.
21. Black, D. A. K., and Thomson, A. E.: Clin. Sc. 10:511, 1951.
22. Blake, W. D.; Wegria, R.; Keating, R. P., and Ward, H. P.: Am. J. Physiol. 157:1, 1949.
23. Blomhert, G.: Over de zogenaamde waterdiurese, Amsterdam, Scheltema and Holkema, 1951; cited in Reference 204.
24. Blomhert, G.; Gerbrandy, J.; Molhuysen, J. A.; de Vries, L. A., and Borst, J. G. G.: Lancet 2:1011, 1951.
25. Bobb, J. R. R.; Lillehei, C. W., and Visscher, M. B.: Fed Proc. 11:15, 1952.
26. Borst, J. G. G.: Acta med. scandinav. (Supp. 207) 130:1, 1948.
27. Bristol, W. R.: Am. J. M. Sc. 221:412, 1951.
28. Brodsky, W. A., and Rapoport, S.: J. Clin. Invest. 30:282, 1951.
29. Brun, C.; Knudsen, E. O. E., and Raaschou, F.: Acta med. scandinav. 122:315, 332, and 486, 1945.

30. Burston, R. A., and Garrod, O.: Clin. Sc. 11:129, 1952.

31. Cargill, W. H.: Proc. Soc. Exper. Biol. & Med. 68:189, 1948.

32. Cizek, L. J., and Huang, K. C.: Am. J. Physiol. 167:473, 1951.

33. Cizek, L. J.; Semple, R. E.; Huang, K. C., and Gregersen, M. I.: Am. J. Physiol. 164: 415, 1951.

34. Collings, W. D.; Downing, C. F., and Hodges, R. E.: Fed. Proc. 8:27, 1949.

35. Collip, J. B., and Backus, P. L.: Am. J. Physiol. 51:568, 1920.

36. Conn, J. W.: J. Lab. & Clin. Med. 45:3, 1955.

37. Conway, E. J., and McCormack, J. I.: J. Physiol. 120:1, 1953.

38. Cooper, I. S., and Crevier, P. H.: J. Clin. Endocrinol. 12:821, 1952.

39. Crawford, B., and Ludemann, H.: J. Clin. Invest. 30:1456, 1951.

40. Danowski, T. S.; Fergus, E. B., and Mateer, F. M.: Ann. Int. Med. 43:643, 1955.

41. Darragh, J. H.; Welt, L. G.; Goodyer, A. V. N., and Abele, W. A.: J. Appl. Physiol. 5:658, 1953.

42. Darrow, D. C., and Yannet, H.: J. Clin. Invest. 14:266, 1935.

43. Darrow, D. C., and Yannet, H.: J. Clin. Invest. 15:419, 1936.

44. Deming, Q. B., and Luetscher, J. A., Jr.: Proc. Soc. Exper. Biol. & Med. 73:171, 1950.

45. Dock, W.: J. A. M. A. 140:1135, 1949.

46. Drury, D. R.; Henry, J. P., and Goodman, J.: J. Clin. Invest. 26:945, 1947.

47. Duncan, L. E.; Bartter, F. C., and Liddle, G. W.: Proceedings of the American Heart Association, New Orleans, 1955, p. 31.

48. Ebert, R. V., and Stead, E. A., Jr.: J. Clin. Invest. 19:561, 1940.

49. Edelman, I. S.; Olney, J. M.; James, A. H.; Brooks, L., and Moore, F. D.: Science 115:447, 1952.

50. Eder, H. A.; Chinard, F. P.; Greif, R. L.; Cotzias, G. C.; Hiller, A.; Van Slyke, D. D., and Lauson, H. D.: J. Clin. Invest. 27:532, 1948.

51. Eggleton, M. G.: J. Physiol. 115:482, 1951.

52. Eggleton, M. G., and Smith, I. G.: J. Physiol. 104:435, 1946.

53. Elkinton, J. R.; Crosley, A. P., Jr.; Barker, H. G., and Clark, J. K.: Fed. Proc. 9:37, 1950.

54. Elkinton, J. R., and Squires, R. D.: Circulation 4:679, 1951.

55. Elkinton, J. R., and Taffel, M.: J. Clin. Invest. 21:787, 1942.

56. Elkinton, J. R.; Winkler, A. W., and Danowski, T. S.: Yale J. Biol. & Med. 17:383, 1944.

57. Elkinton, J. R.; Winkler, A. W., and Danowski, T. S.: J. Clin. Invest. 26:1002, 1947.

58. Epstein, F. H.; Goodyer, A. V. N.; Lawrason, F. D., and Relman, A. S.: J. Clin. Invest. 30:63, 1951.

59. Epstein, F. H.; Post, R. S., and McDowell, M.: J. Clin. Invest. 32:233, 1953.

60. Estes, E. H., and McWhorter, R. L.: Am. J. Physiol. 159:568, 1949.

61. Farber, S. J.; Becker, W. H., and Eichna, L. W.: J. Clin. Invest. 32:1145, 1953.

62. Farber, S. J., and Soberman, R. J.: Proceedings of the American Heart Association, New Orleans, 1955, p. 37.

63. Fishman, A. P.; Stamler, J.; Katz, L. N.; Miller, A. J., and Silber, E. N.: J. Clin. Invest. 29:521, 1950.

64. Fishman, R. A.: J. Clin. Invest. 32:847, 1953.

65. Fitzhugh, F. W., Jr.; McWhorter, R. L., Jr.; Estes, E. H., Jr.; Warren, J. V., and Merrill, A. J.: J. Clin. Invest. 32:1163, 1953.

66. Fox, C. L., Jr.; Friedberg, C. K., and White, A. G.: Am. J. Med. 6:511, 1949.

67. Frank, C. W.; Wang, H.; Lammerant, J.; Miller, R., and Wegria, R.: J. Clin. Invest. 34:722, 1955.

68. Gabuzda, G. J., Jr.; Treager, H. S., and Davidson, C. S.: J. Clin. Invest. 29:814, 1950.

69. Garrod, O.; Davies, S. A., and Cahill, G., Jr.: J. Clin. Invest. 34:761, 1955.

70. Gaudino, M., and Levitt, M. F.: J. Clin. Invest. 28:1487, 1949.

71. Gauer, O. H.; Henry, J. P., and Sieker, H. O.: Proceedings of the 19th International Physiological Congress, Montreal, Canada, 1953, p. 381.

72. Gauer, O. H.; Henry, J. P., and Sieker, H. O., and Wendt, W. E.: J. Clin. Invest. 33: 287, 1954.

73. Gibson, J. G., and Evans, W. A.: J. Clin. Invest. 16:317, 1937.

74. Gilman, A.: Am. J. Physiol. 120:323, 1937.

75. Gilman, A., and Barbour, H. G.: Am. J. Physiol. 104:392, 1933.

76. Goodyer, A. V. N., and Glenn, W. W. L.: Circulation 11:584, 1955.

77. Goodyer, A. V. N., and Glenn, W. W. L.: Am. J. Physiol. 168:66, 1952.

78. Goodyer, A. V. N.; Peterson, E. R., and Relman, A. S.: J. Appl. Physiol. 1:671, 1949.

79. Goodyer, A. V. N., and Seldin, D. W.: J. Clin. Invest. 32:242, 1953.

80. Goodyer, A. V. N., and Seldin, D. W.: J. Clin. Invest. 32:570, 1953.

81. Gordon, E. S.; Chart, J. J., and Meyer, E. S.: J. Clin. Invest. 31:633, 1952.

82. Goudsmit, A., Jr.; Binger, M. W., and Keith, N. M.: Arch. Int. Med. 68:513, 1941.

83. Goudsmit, A.; Power, M. H., and Bollman, J. L.: Proc. Soc. Exper. Biol. & Med. 47: 254, 1941.

84. Green, D. M., and Farah, A.: Am. J. Physiol. 158:444, 1949.

85. Green, D. M., and Farah, A.: Am. J. Physiol. 159:571, 1949.

86. Greene, C. H., and Rowntree, L. G.: Am. J. Physiol. 80:209, 1927.

87. Gross, F., and Gysel, H.: Acta endocrinol. 15:199, 1954.

88. Grossman, J.; Weston, R. E.; Borun, E. R., and Leiter, L.: J. Clin. Invest. 34:1611, 1955.

89. Haldane, J. S., and Priestley, J. G.: J. Physiol. 50:296, 1916.

90. Hall, P. W., III, and Selkurt, E. E.: Am. J. Physiol. 164:143, 1951.

91. Halmágyi, D.: Acta med. scandinav. 137: 150, 1950.

92. Harris, J. F.; Lloyd, C. W., and Lobotsky, J.: J. Clin. Invest. 32:885, 1953.

93. Hartmann, A. F.; Senn, M. J. E.; Nelson, M. V., and Perley, A. M.: J. A. M. A. 100:251, 1933.

94. Henry, J. P., and Gauer, O. H.: Fed. Proc. 10:62, 1951.

95. Henry, J. P.; Gauer, O. H.; Sieker, H. O.; Wendt, W. E.; Reeves, J. L., and Lee, M. F.: Proceedings of the 19th International Physiological Congress, Montreal, Canada, 1953, p. 453.

96. Hetherington, M.: J. Physiol. 73:184, 1931.

97. Hilton, J. G.; Kanter, D. M.; Hays, D. R.; Bowen, E. W.; Golub, J. R.; Keating, J. H., and Wegria, R.: J. Clin. Invest. 34:736, 1955.

98. Holland, B. C.: J. Clin. Invest. 31:639, 1952.

99. Holmes, J. H., and Cizek, L. J.: Am. J. Physiol. 164:407, 1951.

100. Holmes, J. H., and Gregersen, M. I.: Am. J. Physiol. 151:252, 1947.

101. Holmes, J. H., and Gregersen, M. I.: Am. J. Physiol. 162:326, 1950.

102. Holmes, J. H., and Gregersen, M. I.: Am. J. Physiol. 162:338, 1950.

103. Holt, J. P.: Am. J. Physiol. 142:594, 1944.

104. Howarth, S.; McMichael, J., and Sharpey-Schafer, E. P.: Clin. Sc. 6:41, 1946.

105. Hwang, W.; Akman, L. C.; Miller, A. J.; Silber, E. N.; Stamler, J., and Katz, L. N.: Am. J. Physiol. 162:649, 1950.

106. Iseri, L. T.; McCaughey, R. S.; Alexander, L.; Boyle, A. J., and Myers, G. B.: Am. J. M. Sc. 224:135, 1952.

107. Jaenike, J. R., and Waterhouse, C.: Circulation 11:1, 1955.

108. Judson, W. E.; Epstein, F. H.; Tinsley, C. M.; Burrows, B. A., and Wilkins, R. W.: J. Clin. Invest. 29:826, 1950.

109. Judson, W. E.; Hatcher, J. D.; Halperin, M. H., and Wilkins, R. W.: J. Clin. Invest. 31:642, 1952.

110. Judson, W. E.; Hatcher, J. D.; Hollander, W.; Halperin, M. H., and Wilkins, R. W.: J. Clin. Invest. 34:1591, 1955.

111. Kaplan, B. I., and Smith, H. W.: Am. J. Physiol. 113:354, 1935.

112. Keith, N. M.; Rowntree, L. G., and Geraghty, J. T.: Arch. Int. Med. 16:547, 1915.

113. Kerpel-Fronius, O.: Ztschr. Kinderh. 57: 489, 1935.

114. Kleeman, C. R.; Epstein, F. H.; Lamdin, E., and Rubini, M. E.: Clin. Res. Proc. 3:138, 1955.

115. Kottke, F. J.; Code, C. F., and Wood, E. H.: Am. J. Physiol. 136:229, 1942.

116. Ladd, M.: J. Appl. Physiol. 3:379, 1951.

117. Ladd, M.: J. Appl. Physiol. 3:603, 1951.

118. Ladd, M.: J. Appl. Physiol. 4:602, 1952.

119. Laidlaw, J. C.; Dingman, J. F.; Arons, W. L.; Finkenstaedt, J. T., and Thorn, G. W.: Ann. New York Acad. Sc. 61:315, 1955.

120. Lauson, H. D.: Am. J. Med. 11:135, 1951.

121. Lauson, H. D.; Bradley, S. E., and Cournand, A.: J. Clin. Invest. 23:381, 1944.

122. Leaf, A.; Bartter, F. C.; Santos, R. F., and Wrong, O.: J. Clin. Invest. 32:868, 1953.

123. Leaf, A.; Chatillon, J. Y.; Wrong, O., and Tuttle, E. P.: J. Clin. Invest. 33:1261, 1954.

124. Leaf, A., and Mamby, A. R.: J. Clin. Invest. 31:60, 1952.

125. Leiter, L.; Weston, R. E., and Grossman, J.: Bull. New York Acad. Med. 29:833, 1953.

126. Lepore, M. J.: Ann. Int. Med. 11:285, 1937.

127. Levitt, M. F.; Turner, L. B., and Sweet, A. Y.: J. Clin. Invest. 31:885, 1952.

128. Lewis, J. M., Jr.; Buie, R. M.; Sevier, S. M., and Harrison, T. R.: Circulation 2:822, 1950.

129. Lewis, J. M., Jr., and Sevier, S. M.: Am. J. Med. 7:248, 1949.

130. Lewy, F. H., and Gassmann, F. K.: Am. J. Physiol. 112:504, 1935.

131. Liddle, G. W.; Bartter, F. C.; Duncan, L. E., Jr.; Barber, J. K., and Delea, C.: J. Clin. Invest. 34:949, 1955.

132. Lombardo, T. A.: Circulation 7:91, 1953.

133. Lombardo, T. A.; Eisenberg, S.; Oliver, B. B.; Viar, W. N.; Eddleman, E. E., Jr., and Harrison, T. R.: Circulation 3:260, 1951.

134. Lombardo, T. A., and Harrison, T. R.: Circulation 7:88, 1953.

135. Luetscher, J. A., Jr.: J. Clin. Invest. 23: 365, 1944.

136. Luetscher, J. A., Jr., and Axelrad, B. J.: J. Clin. Endocrinol. 14:1086, 1954.

137. Luetscher, J. A., Jr., and Curtis, R. H.: J. Clin. Invest. 34:951, 1955.

138. Luetscher, J. A., Jr., and Johnson, B. B.: J. Clin. Invest. 33:276, 1954.

139. Luetscher, J. A., Jr., and Johnson, B. B.: J. Clin. Invest. 33:1441, 1954.

140. Luetscher, J. A., Jr.; Neher, R., and Wettstein, A.: Experientia 10:456, 1954.

141. Lusk, J. A.; Viar, W. N., and Harrison, T. R.: Circulation 6:911, 1952.

142. Maclean, J. P.; Li, M. C.; Lipsett, M. B.; Ray, B., and Pearson, O. H.: J. Clin. Invest. 34: 951, 1955.

143. Mankin, H., and Lowell, A.: J. Clin. Invest. 27:145, 1948.

144. Martin, S. J.; Herrlich, H. C., and Fazekas, J. F.: Am. J. Physiol. 127:51, 1939.

145. McCance, R. A.: Proc. Roy. Soc., London, s. B 119:245, 1936.

146. McCance, R. A.: Lancet 1:823, 1936.

147. McCance, R. A., and Widdowson, E. M.: J. Physiol. 91:222, 1937.

148. McCance, R. A., and Wilkinson, E.: J. Physiol. 106:256, 1947.

149. McCance, R. A.; Young, W. F., and Black, D. A. K.: J. Physiol. 102:415, 1944.

150. McDowall, R. J. S., and Zayat, A. F.: Proceedings of the 2nd World Congress of Cardiology, Washington, D. C., 1954, p. 102.

151. McMichael, J., and Sharpey-Schafer, E. P.: Brit. Heart J. 6:33, 1944.

152. McWhorter, R. L.; Estes, E. H.; Fitzhugh, F. W., Jr., and Merrill, A. J.: Am. J. Physiol. 159:580, 1949.

153. Miller, G. E.: Circulation 4:270, 1951.

154. Mulinos, M. G.; Spingarn, C. L., and Lojkin, M. E.: Am. J. Physiol. 135:102, 1941.

155. Murphy, R. J. F., and Stead, E. A., Jr.: J. Clin. Invest. 30:1055, 1951.

156. Nadal, J. W.; Pederson, S., and Maddock, W. G.: J. Clin. Invest. 20:691, 1941.

157. Nelson, W. P., III; Rosenbaum, J. D., and Strauss, M. B.: J. Clin. Invest. 30:738, 1951.

158. Netravisesh, V.: J. Appl. Physiol. 5:544, 1953.

159. Ni, T. G., and Rehberg, P. B.: J. Physiol. 71:331, 1931.

160. Nonidez, J. F.: Am. J. Anat. 61:203, 1937.

161. Opie, E. L.: J. Exper. Med. 89:185, 1949.

162. Orloff, J.; Welt, L. G., and Stowe, L.: J. Clin. Invest. 29:770, 1950.

163. Papper, S.; Saxon, L., and Cohen, H. W.: J. Clin. Invest. 34:956, 1955.

164. Pearce, M. L., and Newman, E. V.: J. Clin. Invest. 33:1089, 1954.

165. Peters, J. P.: Body Water, Springfield, Ill., Charles C Thomas, Publisher, 1935, pp. 283-287.

166. Peters, J. P.: New England J. Med. 239: 353, 1948.

167. Peters, J. P.: J. Mt. Sinai Hosp. 17:159, 1950.

168. Peters, J. P.: Am. J. Med. 12:66, 1952.

169. Peters, J. P.; Welt, L. G.; Sims, E. A. H.; Orloff, J., and Needham, J.: Tr. A. Am. Physicians 63:57, 1950.

170. Petersdorf, R. G., and Welt, L. G.: J. Clin. Invest. 32:283, 1953.

171. Phillips, R. A.; Dole, V. P.; Hamilton, P. B.; Emerson, K.; Archibald, R. M., and Van Slyke, D. D.: Am. J. Physiol. 145:314, 1946.

172. Post, R. S.: Am. J. Physiol. 165:278, 1951.

173. Prunty, F. T. G.; McSwiney, R. R.; Mills, I. H., and Smith, M. A.: Lancet 2:620, 1954.

174. Ragan, C.; Ferrebee, J. W.; Phyfe, P.; Atchley, D. W., and Loeb, R. F.: Am. J. Physiol. 131:73, 1940.

175. Relman, A. S., and Schwartz, W. B.: Yale J. Biol. & Med. 24:540, 1952.

176. Renzi, A. A.; Renzi, M.; Chart, J. J., and Gaunt, R.: J. Clin. Endocrinol. 15:853, 1955.

177. Roberts, K. E.; Magida, M. G., and Pitts, R. F.: Am. J. Physiol. 172:47, 1953.

178. Roberts, K. E., and Pitts, R. F.: Endocrinology 50:51, 1952.

179. Robinson, J. R.: Proc. Roy. Soc., London, s. B 137:378, 1950.

180. Roemmelt, J. C.; Sartorius, O. W., and Pitts, R. F.: Am. J. Physiol. 159:124, 1949.

181. Rosenbaum, J. D.; Nelson, W. P., III, and Strauss, M. B.: J. Clin. Invest. 29:841, 1950.

182. Rosenbaum, J. D.; Nelson, W. P., III; Strauss, M. B.; Davis, R. K., and Rossmeisl, E. C.: J. Clin. Invest. 32:394, 1953.

183. Rosenbaum, J. D.; Papper, S., and Ashley, M. M.: J. Clin. Invest. 31:657, 1952.

184. Sala, G., and Luetscher, J. A., Jr.: Endocrinology 55:516, 1954.

185. Sassa, K., and Miyazaki, H.: J. Physiol. 54:203, 1920.

186. Schwartz, B. M.; Smith, P. K., and Winkler, A. W.: Am. J. Physiol. 137:652, 1942.

187. Seldin, D. W., and Tarail, R.: Am. J. Physiol. 159:160, 1949.

188. Selkurt, E. E.; Hall, P. W., and Spencer, M. P.: Am. J. Physiol. 157:40, 1949.

189. Selkurt, E. E.; Hall, P. W., and Spencer, M. P.: Am. J. Physiol. 159:369, 1949.

190. Shannon, J. A.: J. Exper. Med. 76:371, 1942.

191. Shipley, R. E., and Study, R. S.: Am. J. Physiol. 167:676, 1951.

192. Sieker, H. O.; Gauer, O. H., and Henry, J. P.: J. Clin. Invest. 33:572, 1954.

193. Simmons, D. H.; Harvey, R. B., and Hoshiko, T.: Am. J. Physiol. 178:182, 1954.

194. Simpson, G. E.: J. Biol. Chem. 84:393, 1929.

195. Simpson, S. A.; Tait, J. F.; Wettstein, A.; Neher, R.; Von Euw, J., and Reichstein, T.: Experientia 9:333, 1953.

196. Smith, H. W.: The Physiology of the Kidney, London, Oxford University Press, 1937, p. 150.

197. Smith, H. W.: Fed. Proc. 11:701, 1952.

198. Squires, R. D.; Singer, R. B.; Moffitt, G. R., Jr., and Elkinton, J. R.: Circulation 4: 697, 1951.

199. Stanbury, S. W., and Thomson, A. E.: Clin. Sc. 11:357, 1952.

200. Starling, E. H.: The Fluids of the Body, The Herter Lectures, Chicago, W. T. Keener and Co., 1909.

201. Stevenson, J. A. F.; Welt, L. G., and Orloff, J.: Am. J. Physiol. 161:35, 1950.

202. Stewart, J. D., and Rourke, G. M.: J. Clin. Invest. 15:697, 1936.

203. Stewart, J. D., and Rourke, G. M.: J. Clin. Invest. 21:197, 1942.

204. Strauss, M. B.; Davis, R. K.; Rosenbaum, J. D., and Rossmeisl, E. C.: J. Clin. Invest. 30:862, 1951.

205. Strauss, M. B.; Davis, R. K.; Rosenbaum, J. D., and Rossmeisl, E. C.: J. Clin. Invest. 31:80, 1952.

206. Strauss, M. B.; Rosenbaum, J. D., and Nelson, W. P., III: J. Clin. Invest. 29:1053, 1950.

207. Tales from the Arabian Nights: The Fifth Voyage of Sindbad the Seaman, translated by Sir Richard Burton, 885-888; reprinted by Pocket Books, Inc., n. d.

208. Tarail, R., and Logsdon, G. R.: J. Clin. Invest. 32:607, 1953.

209. Thompson, W. H.: J. Physiol. 25:487, 1900.

210. Thompson, W. O.; Thompson, P. K., and Dailey, M. E.: Proc. Nat. Acad. Sc. 14:94, 1928.

211. Verney, E. B.: Proc. Roy. Soc., London, s. B 135:25, 1947.

212. Viar, W. N.; Oliver, B. B.; Eisenberg, S.; Lombardo, T. A.; Willis, K., and Harrison, T. R.: Circulation 3:105, 1951.

213. Warren, J. V.; Brannon, E. S.; Stead, E. A., Jr., and Merrill, A. J.: J. Clin. Invest. 24:337, 1945.

214. Warren, J. V., and Stead, E. A., Jr.: Arch. Int. Med. 73:138, 1944.

215. Welt, L. G.: A. M. A. Arch. Int. Med. 89:931, 1952.

216. Welt, L. G., and Orloff, J.: J. Clin. Invest. 30:751, 1951.

217. Welt, L. G.; Seldin, D. W.; Nelson, W. P.; German, W. J., and Peters, J. P.: A. M. A. Arch. Int. Med. 90:355, 1952.

218. Werkö, L.; Ek, J.; Bucht, H., and Varnauskas, E.: Proceedings of the 2nd World Congress of Cardiology, Washington, D. C., 1954, p. 103.

219. Wesson, L. G., Jr.; Anslow, W. P., Jr.; Raisz, L. G.; Bolomey, A. A., and Ladd, M.: Am. J. Physiol. 162:677, 1950.

220. Wesson, L. G., Jr.; Anslow, W. P., Jr., and Smith, H. W.: Bull. New York Acad. Med. 24:586, 1948.

221. West, C. D.; Traeger, J., and Kaplan, S. A.: J. Clin. Invest. 34:887, 1955.

222. Weston, R. E.; Borun, E. R.; Grossman, J.; Guerin, H. A.; Ullman, T. D.; Wolfman, M., and Leiter, L.: Proc. Am. Heart A. 25:13, 1952.

223. Weston, R. E.; Hanenson, I. B.; Borun, E. R.; Grossman, J., and Wolfman, M.: J. Clin. Invest. 31:672, 1952.

224. Weston, R. E.; Hanenson, I. B.; Grossman, J.; Berdasco, G. A., and Wolfman, M.: J. Clin. Invest. 32:611, 1953.

225. Weston, R. E.; Hanenson, I. B.; Grossman, J.; Horowitz, H. B.; Wolfman, M., and Leiter, L.: Fed. Proc. 13:163, 1954.

226. White, H. L.; Rosen, I. T.; Fischer, S. S., and Wood, G. H.: Am. J. Physiol. 78: 185, 1926.

227. Whitteridge, D.: Physiol. Rev. 30:475, 1950.

228. Wilkins, R. W.; Tinsley, C. M.; Culbertson, J. W.; Burrows, B. A.; Judson, W. E., and Burnett, C. H.: J. Clin. Invest. 32:1101, 1953.

229. Williams, T. F.; Hollander, W., Jr.; Strauss, M. B.; Rossmeisl, E. C., and McLean, R.: J. Clin. Invest. 34:595, 1955.

230. Wilson, G.; Edelman, I. S.; Brooks, L.; Myrden, J. A.; Harken, D. E., and Moore, F. D.: Circulation 9:199, 1954.

231. Winter, C. A.; Ingram, W. R., and Eaton, R. C.: Am. J. Physiol. 139:700, 1943.

232. Winter, C. A.; Ingram, W. R., and Gross, E. G.: Am. J. Physiol. 127:64, 1939.

233. Winter, C. A.; Sattler, D. G., and Ingram, W. R.: Am. J. Physiol. 131:363, 1940.

234. Wolf, A. V.: Am. J. Physiol. 161:75, 1950.

Case Reports

Neurogenic Nephropathy

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Alterations in renal function and structure originating in the central nervous system have received scant attention in clinical medicine. To be sure, it has long been known that emotion may be manifested by proteinuria and that the latter, in massive form, may result from disease of the brain, notably subarachnoid hemorrhage. In this communication, an observation is recorded showing that brain disease may bring about severe renal failure. Evidence will also be adduced that these renal manifestations of cerebral origin, extending from trivial proteinuria to renal insufficiency causing uremia, are all produced through the intermediacy of renal vasoconstriction.

Report of Case

On Dec. 22, a previously healthy man of 33 years suddenly had a clonic convulsion and fell to the floor in coma. Clonic convulsions were repeated at short intervals. He was brought to Beth Israel Hospital about 45 minutes after the initial convulsion, still in coma.

In the past history, elicited several days after admission, the only item of possible relevance was that five years previously, while in the Marine Corps, he had been unconscious for several minutes after striking his head against a wall. A lumbar puncture at the time was said to have been negative, and he had felt well thereafter. Careful inquiry disclosed no evidence of past renal disease.

Generalized clonic convulsions were still recurring at intervals of a few minutes after the comatose patient had been admitted. They were terminated by the intravenous injection of thiopental (Pentothal) sodium. The patient did not respond to painful stimuli. The neck was not stiff. The deep reflexes were present. There were no focal neurological signs. Ophthalmoscopic examination was negative. Lumbar puncture revealed grossly bloody fluid, and a diagnosis of subarachnoid hemorrhage was made. The patient began to move his extremities about four hours after admission and by a few hours later had recovered consciousness.

The first blood pressure reading was made by a nurse a few minutes after admission; the systolic pressure was 160 mm. of Hg. A few minutes later I found the blood pressure to be 170/115 mm. Subsequent blood pressure readings are listed in the Table. At no time was there any evidence of shock; the physician who gave him emergency treatment within a few minutes of the onset found his pulse strong, the extremities warm, and sweating absent.

During the first hospital day the patient was incontinent and passed "a small amount of urine," apparently well under 100 ml. The following day he did not void, and on the fourth day 400 ml. was obtained by catheter, constituting the urinary volume for the two days. The urinary output is shown in the Table.

During the first days of his illness the patient was disoriented part of the time and tormented by hiccough, nausea, and occasional vomiting. Fever developed was found to be due to a pneumonic consolidation in the left lower lobe. Cardiac weakness was documented by presystolic gallop rhythm. A pericardial rub was audible for two days and attributed to uremic pericarditis. Repeated lumbar taps revealed diminishing numbers of red cells and xanthochromia; manometric readings were not abnormal. The electroencephalogram was interpreted by Dr. Mortimer Ostow to indicate "dysfunction of the diencephalic centers which is seen in cases of subarachnoid hemorrhage, and with metabolic disturbances."

During the first days of the illness, fluid was administered intravenously. The attempt was made to keep the fluid intake approximately 1000 ml. daily more than the fluid loss by all routes, with an added allowance of 300 ml. for each degree of fever. When hyponatremia and

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From the Medical Service of Beth Israel Hospital.

Laboratory Data

Date	Urine				Serum N.P.N. Mg./100 Ml.	Blood Pressure Mm. Hg
	Volume, Ml.	Specific Gravity	Proteinuria	Erythrocytes H.P.F.		
12/23	120	1.020	3+	8–15	53	168/94
12/24				"rare"		160/100
12/25	400	1.024	3+			140/100
12/26	200	1.014	3+	8–10		170/100
12/27	330				170	156/100
12/28	650				175	150/90
12/29	720	1.008	2+	1–5	185	140/86
12/30	460	1.008	1+	3–9	230	150/90
12/31	1350	1.008	0	3	220	170/96
1/1	1440					154/92
1/2	1590					160/84
1/3	1825	1.010	Tr.	40–50	215	170/100
1/4	2910	1.010	Ft. tr.	1–3	290	158/98
1/5	4675	1.006	Ft. tr.	8–12	258	168/80
1/6	6695	1.006	Ft. tr.	25–35	210	168/90
1/7	7645	1.008	Ft. tr.	6–11	185	160/88
1/8	9140					174/94
1/9	8870				170	170/92
1/10	7070				145	158/88
1/11	5610				135	158/86
1/12	6040	1.003	Ft. tr.	0	135	166/88
1/16	4480				105	170/104
1/20	3820				50	140/90
7/6		1.014	0	0	33	138/90
9/5					30	132/84

hypochloremia were found, 0.9% NaCl was added to the dextrose in the infusion; for two days this was supplemented by administration of 200 ml. daily of 5% NaCl solution. Antibiotics were given, and the patient was digitalized when gallop rhythm appeared.

The patient was discharged Jan. 24, feeling entirely well. However, a concentration test at this time revealed a maximum specific gravity of 1.007.

May 24, the patient had a generalized convulsion with a brief period of unconsciousness. He was readmitted to Beth Israel Hospital. At this time, urinalysis was negative and the nonprotein nitrogen of the serum was 33 mg. per 100 ml. The right carotid arteriogram revealed depression of the right anterior cerebral artery. The pneumoencephalogram disclosed displacement of the ventricular system to the left and of the right lateral horn downward, indicating a frontal lesion on the right side. The patient elected to postpone operation until September. Dr. Leo Davidoff then removed a large frontal parasagittal tumor (microscopic diagnosis, glioblastoma multiforme), but the patient died the next day.

At necropsy, the kidneys revealed no significant changes. Apart from one small area of fibrosis, both glomeruli and tubules were intact (Dr. William Antopol). The histological findings afforded no hint of the extreme renal failure present 10 months previously.

Comment

The acute renal insufficiency in this case passed through four stages: (1) Oliguria with normal specific gravity; (2) oliguria with low specific gravity (hyposthenuria); (3) onset of recovery with tremendous polyuria (surpassing 9000 ml. daily); (4) a period of hyposthenuria lasting months, during which the kidneys attained the morphological normality found at necropsy.

These are precisely the four stages seen in typical cases of acute renal insufficiency resulting from hypotension in shock, for example, in the crush syndrome or other forms of oligemic shock. In shock it appears [1] that these four stages of acute renal insufficiency have the following substrata: (1) Oliguria with high specific gravity occurs at the onset when low arterial pressure lessens renal blood flow and glomerular filtration, while tubular function is still relatively intact. (2) The succeeding stage of oliguria with low specific gravity manifests the addition of ischemic damage to the tubules so severe that there is solution of continuity of the tubular cells [2] with consequent nonselective back-diffusion of the glomerular filtrate; the little that escapes as urine is of low specific gravity because of impairment of tubular concentration. (3) Great polyuria appears when the tubular cells have regenerated sufficiently to prevent nonselective back-diffusion but have not regained their full capacity for active reabsorption and while the diuretic stimulus of

retained urea still operates. (4) the final stage of hyposthenuria with slight polyuria manifests the remarkably long time the regenerated tubular cells require to regain their full concentrating ability.

In this case, however, the renal damage was not due to arterial hypotension. Not only were hypotension and clinical shock absent, but frequent measurements beginning less than an hour after the onset showed that arterial pressure was always elevated above the level which observations after recovery showed to be the patient's normal. Since the identity of the pattern of the renal insufficiency with that seen in shock, the absence of evidences of glomerulonephritis, and the subsequent finding of normal kidneys at necropsy all point to an ischemic causation of the renal failure, the presence of hypertension from the very start immediately suggests renal vasoconstriction as the pathogenetic mechanism. When hypertension results from acute tubular necrosis, as in the crush syndrome or in mercury poisoning, I have never seen it before the third or fourth day. In the following, clinical and experimental evidence will be cited which indicates that ischemic renal damage may result from renal vasoconstriction triggered in the brain.

Urinary Changes and Impaired Renal Function of Cerebral Origin

Emotional Proteinuria.—It was already known in the 19th century that students not rarely exhibit transitory proteinuria before examinations.[3] Proteinuria appeared in 504 of 1000 healthy cadets after venipuncture for a Kahn test; all but 3 of the 127 who felt faint or fainted developed proteinuria.[4]

Meningeal Hemorrhage.—Widal[5] long ago observed more than 2 gm. of protein per liter in the urine of a patient with subarachnoid hemorrhage. Proteinuria of high degree appears only in severe episodes, almost always of fulminating onset, in which the patient is comatose or is aroused only with difficulty. Repeated examinations of the urine disclosed transitory massive proteinuria in 3 of 10 such cases; slight proteinuria was present in 3 others in at least one examination. Protein may appear in the urine less than an hour after the onset of the attack and quickly become massive; the urine may boil solid and contain even more than 3% of protein. The proteinuria quickly diminishes and has usually vanished in less than a week; chronic proteinuria does not result. The very transient duration of proteinuria so massive is most striking in some of the cases and rarely encountered under other circumstances. Microscopic examination of the albuminous urine may be almost negative, or there may be a few red cells and hyaline and granular casts, which soon disappear.

The severity with which renal function may be impaired in subarachnoid hemorrhage is illustrated in the case reported. In another case of subarachnoid hemorrhage with slight elevation of blood pressure and no shock, the blood urea nitrogen exceeded 60 mg. per 100 ml. Azotemia in subarachnoid hemorrhage has been previously observed.[6,7]

Epilepsy.—Proteinuria is very common in the first hours after an attack of grand mal; it is almost always present during status epilepticus. The proteinuria is transient, but may be so massive that the urine boils solid. In a woman with mitral stenosis and "idiopathic" epilepsy, massive proteinuria (1.8% on one occasion) was present after four different convulsive seizures months apart; it disappeared within 48 hours each time.

Brain Tumor.—Schmidt[8] observed oliguria and demonstrated diminished ability of the kidneys to excrete water in some patients with high intracranial pressure due to brain tumor.

Ventriculography and Pneumoencephalography.—In 10 patients, Weinberg and coworkers[9] observed decrease in renal water, chloride, and nitrogen excretion during these tests.

Renal Ischemia of Cerebral Origin

Experimental observations leave no doubt that appropriate stimuli acting on the brain

produce renal vasoconstriction and consequent renal ischemia of high degree. Smith [10] observed profound depression of renal blood flow (iodopyracet [Diodrast] clearance) in a man who became frightened. Wolf [11] found that when severe pain was produced by pressure on the skull in man, both renal blood flow and glomerular filtration fell *pari passu* with rise in blood pressure. In Green and Hoff's [12] experiments, stimulation of the motor and premotor areas of monkeys and cats produced simultaneous diminution in renal and increase in limb volume, i. e., renal vasoconstriction. Starr [13] showed that various techniques of producing renal vasoconstriction in man and the cat result in proteinuria. King and Baldwin [14] found that the intravenous injection of epinephrine and arterenol in man produces decrease in renal blood flow and proteinuria which lasts up to 50 minutes after the injection has been terminated.

Neurogenic Nephropathy

In each of the aforementioned circumstances—strong emotion, subarachnoid hemorrhage, grand mal, and acute rise in intracranial pressure due to brain tumor—evidences of injury to the kidneys may appear. When of emotional origin, the renal manifestations consist of no more than slight and transitory proteinuria of only academic interest. The same is most often true of the renal damage due to the acute cerebral episodes, but in these the proteinuria may become massive, and in rare instances there may be acute renal insufficiency with azotemia and uremia which completely dominates the clinical picture. As the case described illustrates, the renal damage is completely reversible; there is no evidence that chronic kidney disease ever results. In all instances it appears that the renal injury is produced through the intermediacy of renal vasoconstriction of cerebral origin with consequent ischemia and may be appropriately termed neurogenic nephropathy.

While neurogenic nephropathy is rarely severe enough to be of clinical importance, it has theoretical significance in that it exemplifies disease resulting from exaggeration of a homeostatic and ordinarily beneficent mechanism. The kidneys are remarkable in that they receive more than one-quarter of the cardiac output. Since curtailment of renal function is not an immediate menace to survival, the renal blood flow furnishes a reserve supply of blood that, in case of emergency, can be diverted elsewhere. Ordinarily, the sympathetic vasomotor innervation of the kidneys is at rest [11] but is called into action under circumstances in which sympathetic stimulation occurs, for example, fright. This is doubtless the explanation of emotional proteinuria, and the more intense pathological stimulation of the same sympathetic vasomotor mechanism in such conditions as subarachnoid hemorrhage and grand mal produces the severer forms of neurogenic nephropathy.

Summary

A case of renal insufficiency with uremia associated with subarachnoid hemorrhage is described. The case exemplifies the extreme form of renal damage of cerebral origin, of which emotional proteinuria is the mildest gradation, and massive proteinuria in subarachnoid hemorrhage and grand mal represent varieties of intermediary intensity. Available evidence indicates that in all these conditions the injury to the kidney, here termed neurogenic nephropathy, is ischemic in pathogenesis and due to neurogenic renal vasoconstriction.

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REFERENCES

1. Fishberg, A. M.: Hypertension and Nephritis, Ed. 5, Philadelphia, Lea & Febiger, 1954, pp. 77, 78, and 414.

2. Oliver, J.; MacDowell, M., and Tracy, A.: The Pathogenesis of Acute Renal Failure Associated with Traumatic and Toxic Injury, J. Clin. Invest. 30:1305-1438 (Dec.) 1951.

3. Clark, A.: On Albuminuria, Brit. M. J. 2:312 (Aug. 6) 1884.

4. Ahronheim, J. H.: Emotional Albuminuria, War Med. 5:267-270 (May) 1944.

5. Widal, F.: Le Diagnostic de l'hémorrhagie méningée, Presse méd. 1:413-415 (June 3) 1903.

6. Guillain, G., and Vincent, C.: Valeur séméiologique de l'albuminurie dans les hémorrhagies méningées, Semaine méd. 29:505-508 (Oct. 27) 1909.

7. Morawitz, P., and Schloss, J.: "Extrarenale" Albuminurie und Urämie, Klin. Wchnschr. 11:1628-1632 (Sept. 24) 1932.

8. Schmidt, R.: Über Hirntumor-Oligurie, Klin. Wchnschr. 12:105-106 (Jan. 21) 1933.

9. Weinberg, S. J.; Goodman, J. R., and Bushard, M. C.: Alterations in Renal Function, Including Hematuria, in Man During Intracranial Air Studies, Arch. Int. Med. 86:857-871 (Dec.) 1950.

10. Smith, H. W.: The Kidney, New York, Oxford University Press, 1951, Chap. 14.

11. Wolf, G. A.: The Effect of Pain on Renal Function, A. Res. Nerv. & Ment. Dis., Proc. (1942) 23:358-363, 1943.

12. Green, H. D., and Hoff, E. C.: Effect of Faradic Stimulation of the Cerebral Cortex on Limb and Renal Volumes, Am. J. Physiol. 118:641-658 (April) 1937.

13. Starr, I.: The Production of Albuminuria by Renal Vasoconstriction in Animals and in Man, J. Exper. Med. 43:31-51 (Jan.) 1926.

14. King, S. E., and Baldwin, D. S.: Production of Renal Ischemia and Proteinuria in Man with Intravenous L-Norepinephrine and Epinephrine, J. Clin. Invest. 34:945 (June) 1955.

Important Diagnostic Signs of a Leaking Abdominal Aortic Aneurysm

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Abdominal aortic aneurysms present a difficult diagnostic problem when they rupture into the retroperitoneal space. Frequently the diagnosis is made only at operation or at death. Symptoms and signs may mimic an acute surgical abdomen and may suggest a perforated viscus, renal calculus, retroperitoneal abscess, strangulated hernia, or mesenteric vascular occlusion.[1,2,3] With the advent of homograft replacement, not only have intact abdominal aortic aneurysms been repaired, but ruptured ones have as well.[4] This fact, coupled with the fact that there is often a significant time interval from the onset of leaking to ultimate rupture, make it important to recognize this entity. The case presented below is unusual in that there were few abdominal symptoms and that the slowly leaking aneurysm ran a clinical course compatible with an infection or fever of undetermined etiology.

Report of Case

A 66-year-old single white man was admitted for the first time to the Salem Hospital on July 13, 1953, and he died Aug. 11, 1953. He gave a history of chronic alcoholism, including several episodes of delirium tremens and a suicidal attempt in 1928. There was no other history of significant illness. He lived alone, ate poorly, and was on a drinking spree three weeks before entry. The patient appeared at the outpatient clinic on June 30, with a five-day history of crusted sores about his lips and nares that was diagnosed as hemorrhagic impetigo, with Staphylococcus aureus and Bacillus pyocyaneus growing on culture. The temperature was 100.6 degrees F, blood hemoglobin 10.5 gm. per 100 cc., and white blood cell count 9450. Polymixin ointment was applied locally and penicillin, 400,000 units I. M., given for three days.

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From the Medical Service of the Salem Hospital, Salem, Mass.

When the patient was seen two weeks later, his mouth lesions had healed, but he complained of severe weakness and was febrile. Because of this he was admitted to the hospital.

He complained of anorexia but denied nausea, vomiting, constipation, or signs of gastrointestinal bleeding. There was no abdominal or back pain. On physical examination the patient was slightly confused but was oriented. He looked chronically ill but was moderately well nourished. Weight was 121 lb., temperature 100 degrees F, pulse 110, blood pressure 130/70, and respirations 24. There was evidence of the healed impetigo infection on his lips. The chest was clear, and the heart was not enlarged. A nontender liver edge was palpable 2 fingerbreadths below the right costal margin. No other abdominal masses were felt. Genitalia and rectal examination were negative. There was no ankle edema, and pedal pulses were present.

Laboratory examination showed a leukocytosis of 27,600, with 85% neutrophiles, 9% small lymphocytes, and 6% monocytes. Hemoglobin was 10.8 gm. per 100 cc., red blood cell count 3.2 million, and hematocrit 35%, with slight macrocytosis on smear. Urinalysis was negative except for an occasional white cell. Five stool examinations were negative for occult blood, and there were no ova or parasites. Blood Hinton was negative, as was the spinal fluid Wassermann. A Combs test was negative. Blood nonprotein nitrogen was 30 mg.: glucose, 110 mg.; erythrocyte sedimentation rate, 1.9 mm/minute, and total protein 7.8 gm. per 100 cc., with 2.7 gm. of albumin. Liver function tests were as follows: sulfobromophthalein (Bromsulphalein) test 70% in 45 minutes, 30% on repeat examination; cephalin flocculation 1+; thymol turbidity 3 units; alkaline phosphatase 6.6 Bodansky units; serum bilirubin too low to read; serum amylase normal at 8 units, and prothrombin time 16.2 seconds, with control 14.5 seconds.

The patient's hospital course was characterized by a continuing fever in the range of 100 to 101 degrees F by rectum, going as high as 104, accompanied by a persistant leukocytosis of 18,000 to 20,000. Because of these findings, an intensive search was made for a hidden infection. Nine paired blood cultures were done and were negative except for growth of contaminants in two

nonpaired flasks. Urine culture showed Escherichia coli, S. aureus and Aerobacter aerogenes, while stool culture was negative for pathogens. Lumbar puncture was normal, as were two bone marrow aspirations, except for a slight increase in plasma cells in one. Serum agglutination tests for brucellosis, typhoid, paratyphoid, and tularemia were negative. Results of a biopsy of the gastrocnemius muscle were normal. X-ray examinations, including a chest film, abdominal film, upper gastrointestinal series, and intravenous pyelogram, were normal except for "some calcification of the abdominal aorta and its branches."

The cause of fever remained an enigma. Although the impetigo had cleared, it was argued that there might be a metastatic focus of infection. Therapeutic doses of sulfisoxazole (Gantrisin), penicillin, streptomycin, oxytetracycline, and chloramphenicol were each given for periods of three to four days without effect on temperature.

On July 27, in three days' time, the blood hemoglobin and red blood cell count dropped from 11.1 to 7.8 gm. per 100 cc. and 3.6 to 2.6 million, respectively. There was no evidence of blood loss via the gastrointestinal tract, the stools being guaiac negative, and there were on symptoms save chills. Blood pressure declined slightly from 110/60 to 90/50, while the pulse remained in the range of 110. Hemoglobin increased to 11.4 gm. per 100 cc. and blood pressure to 110/60 with a transfusion of 1000 cc.

On Aug. 3, a detailed physical examination demonstrated a slightly tender deeply situated mass in the left epigastrium. The mass was approximately 10 cm. in diameter, it was firm with expansible pulsation, and a Grade 2 systolic bruit was heard over it. No spasm was present, and peristalsis was normal. The pulses in the left leg were less than the right, while the blood pressure in the right arm was 110/70 compared to 104/68 in the right leg. The diagnosis of an abdominal aortic aneurysm was made, with leakage of blood into the retroperitoneal space to account for fever, leukocytosis and hemoglobin drop.

A barium enema and repeat gastrointestinal series were done, showing a soft tissue mass measuring 13 cm. in diameter, centering on the third lumbar vertebra. There was a thin irregular line to the left of the spinal column, presumably representing calcification in the wall of the abdominal aorta. Reference to films taken 10 days previously suggested that the calcium was displaced more laterally. No erosion of the lumbar vertebrae was seen, but there was displacement upward of the horizontal loop of the duodenum.

Surgical opinion favored the possibility of abscess in addition to the aneurysm, and after a transfusion of 500 cc. of blood, the patient was explored on Aug. 7. A large pulsatile mass was found in the retroperitoneal space, extending from the duodenum to the level of the iliac bifurcation. Bright red blood was aspirated from the lateral aspects of the mass; this was cultured with no growth of organisms. No abscess was found. The operation was concluded after a liver biopsy was done that showed a slight increase of lymphocytes and neutrophiles in the portal areas, with fatty vacuolization of liver cells.

Paralytic ileus with vomiting developed but subsided two days postoperatively. On Aug. 10, the patient went into sudden shock, with blood pressure falling to 70/54, pulse 130, respirations 48, temperature 103.5 degrees F, and hemoglobin 10.4 gm. per 100 cc. There was no abdominal pain or vomiting. Peristalsis was diminished; voluntary spasm and shifting dullness in the left flank were present. Six hours after onset of shock the patient died despite transfusion, with the diagnosis of ruptured abdominal aortic aneurysm.

At autopsy an estimated 500 to 800 cc. of serosanguinous fluid was in the peritoneal cavity, with the abdominal viscera displaced anteriorly by a large retroperitoneal mass. Between the renal arteries and iliac bifurcation of the aorta, a saccular aneurysm was found measuring 10 cm. in diameter. The wall of the aneurysm was covered by layered antemortem clot, but the lumen and branches were patent. At the right posterior aspect of the aneurysm was a small necrotic area believed to be the point of rupture.

An estimated 1800 cc. of blood clots surrounded the aneurysm, extending to the subserosal aspect of the cecum and into the gastrohepatic ligament. Erosion was found at the left lateral aspects of the lower part of the second and upper part of the third lumbar vertebrae.

Adhesions were found at the lung apices, and a minimal amount of serous pleural fluid was present. The lungs were normal except for a dark brown area at the surface of the right lower lobe, which extruded sanguinous fluid when cut. The heart weighed 450 gm. and had normal valves and a moderate amount of coronary atherosclerosis. The spleen weighed 75 gm.; the liver was slightly pale with a smooth surface and homogeneously brown on cut section. The gastrointestinal tract contained no blood or other abnormality; the gall bladder, adrenals, kidneys, pancreas, prostate, and bladder were normal.

Microscopic study revealed that the abdominal aorta had areas of cholesterol deposition and calcium in its wall, consistent with atherosclerosis. In its wall at the point of rupture was a neutrophilic infiltrate and tissue necrosis. Slight periportal fibrosis and centrilobular congestion was present. There was a moderate amount of vacuolization of hepatic cells, with a few focal collections of acute inflammatory cells. Lungs showed dilated

alveoli and scattered areas with red cells, mononuclears, and neutrophiles in the alveoli. Nephrosclerosis was present, with thickening and hyalinization of vessel walls, as well as a few hyalinized glomeruli. Microscopically, the heart, spleen, stomach, adrenals, pancreas, and bone marrow were negative.

Comment

A 66-year-old man was found to have a ruptured atherosclerotic abdominal aneurysm. The diagnosis of a leaking aneurysm was made only a week before death after three weeks of unexplained fever. The fever of 101 to 103 degrees F, the drop in blood hemoglobin, and leukocytosis was explained on the basis of slow retroperitoneal hemorrhage (Fig. 1). Until this diagnosis was made, many studies, including cultures and x-rays, failed to determine the cause of fever. However, a later review of films showed evidence of an enlarging retroperitoneal mass (Fig. 2). Four days before death surgical exploration revealed the aneurysm. At autopsy there was no evidence for other disease except an atelectatic lung lobe and minimal portal cirrhosis.

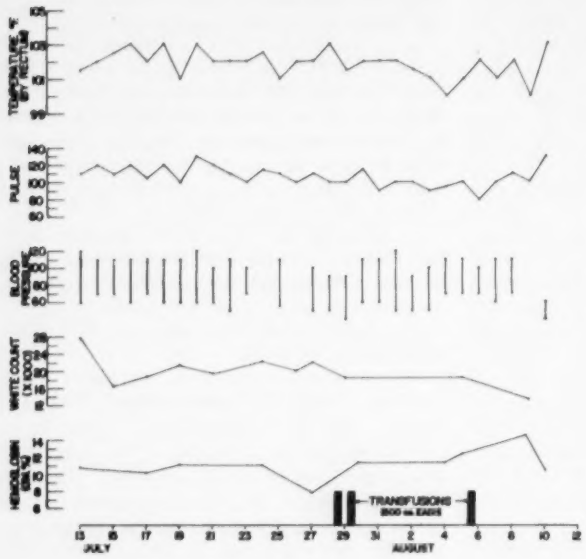

Fig. 1.—Chart depicting the clinical course of a 66-year-old man with a ruptured abdominal aortic aneurysm.

The classical clinical features of an unruptured abdominal aortic aneurysm are well known and consist of pain, an expansile pulsating mass, bruit, erosion, and calcification by x-ray.[5-7] When the aneurysm ruptures, however, the rapidity of the hemorrhage and its location lead to varying signs and symptoms. Although an abdominal atherosclerotic or syphilitic aneurysm may rupture into the peritoneal space, pleural cavity, or gastrointestinal tract, the commonest site of rupture is into the retroperitoneal space.[2,5,8,9] With retroperitoneal rupture, pain is almost a universal complaint, and syncope or shock may occur. Pain may be felt in the abdomen or back, be generalized, or radiate to the groin or leg.[1,4,9,10] Peritoneal irritation with boardlike rigidity and abdominal distention are frequent findings. An x-ray demonstrating an increase in size of the soft-tissue mass with hematoma shadow surrounding the calcified aneurysmal wall or obliteration of the psoas shadow would point to retroperitoneal hemorrhage.[4,11] Many authors have stressed that there is an interval from the onset of leaking to final rupture of two to six days or longer.[4,5,9,12,14] This delay in the rate of hemorrhage has been explained by a tamponade effect exerted by the firm

Fig. 2.—Comparison of intravenous pyelogram on July 24, 1953 (*A*) and barium enema on Aug. 4, 1953 (*B*), with arrows pointing to outline of aneurysm.

retroperitoneal tissues.[8,14] The importance of slow leaking is that the physician is given a few days grace to initiate surgical therapy before ultimate rupture.

When there is less rapid bleeding into the retroperitoneal area, as in the case above, the signs of a leaking abdominal aneurysm are less dramatic. Signs of tissue destruction may predominate, with fever and a leukocytosis together with a progressive anemia, as blood is lost into the surrounding tissues. Although the fever tends to be low grade, the white cell count may be high. Goldowsky found a leukocytosis in 9 out of 10 recorded instances of ruptured abdominal aneurysm, and 5 patients had white cell counts above 20,000.[13] It is therefore important to recognize that a progressive anemia and unexplained fever or leukocytosis in a patient with an abdominal aortic aneurysm are signs of blood leaking into the retroperitoneal space that may presage exsanguination.

Summary

A case of abdominal aortic aneurysm with rupture into the retroperitoneal space is described. Although fever, leukocytosis, and progressive anemia suggested infection, none was found by culture or at postmortem examination. These signs in a patient with an abdominal aneurysm should alert the physician to the possibility of slow retroperitoneal hemorrhage.

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REFERENCES

1. Lipshutz, B., and Chodoff, R. J.: Diagnosis of Ruptured Abdominal Aortic Aneurysm: Report of a Case, Arch. Surg. 39:171-181 (Aug.) 1939.

2. Jump, H. D., and Leaman, W. G., Jr.: Abdominal Aortic Aneurysm: Its Incidence, Diagnosis, Complications and Treatment with Report of a Case Showing Terminal Rupture of the Aorta Posterior to the Aneurysmal Sac, Internat. Clin. 1:166-179 (March) 1939.

3. Uhle, C. A. W.: The Significance of Aneurysm of the Abdominal Aorta Masquerading as Primary Urologic Disease, J. Urol. 45:13-40 (Jan.) 1941.

4. Cooley, D. A., and DeBakey, M. E.: Ruptured Aneurysms of Abdominal Aorta: Excision and Homograft Replacement, Postgrad. Med. 16:334-342 (Oct.) 1954.

5. Kampmeier, R. H.: Aneurysm of the Abdominal Aorta: A Study of 73 Cases, Am. J. M. Sc. 192:97-109 (July) 1936.

6. Scott, V.: Abdominal Aneurysms: A Report of 96 Cases, Am. J. Syph. 28:682-710 (Nov.) 1944.

7. Estes, J. E.: Abdominal Aortic Aneurysm: A Study of 102 Cases, Circulation 2:258-264 (Aug.) 1950.

8. Hirschowitz, B. I., and Bagg, L.: Aneurysm of the Abdominal Aorta with a Report of 4 Unusual Cases, Gastroenterology 18:361-376 (July) 1951.

9. Copping, G. A.: Spontaneous Rupture of Abdominal Aorta, J. A. M. A. 151:374-376 (Jan. 31) 1953.

10. Karabin, J. E.: Retroperitoneal Hemorrhage, with Special Reference to the Accompanying Paralytic Ileus, Am. J. Surg. 56:471-479 (May) 1942.

11. Grayson, C. E., and Kennedy, B. R.: Roentgen Diagnosis of Ruptured Aneurysm of the Abdominal Aorta, Radiology 54:413-416 (March) 1950.

12. Blakemore, A. H.: The Clinical Behavior of Arteriosclerotic Aneurysm of the Abdominal Aorta: A Rational Surgical Therapy, Ann. Surg. 126:195-207 (Aug.) 1947.

13. Goldowsky, S. J.: Spontaneous Rupture of the Abdominal Aorta, Rhode Island M. J. 35:604-606 (Nov.) 1952.

14. Lazarus, J. A., and Marks, M. S.: Aneurysm of the Abdominal Aorta Associated with Urinary Symptoms, J. Urol. 52:115-125 (Aug.) 1944.

Thrombocytopenia Due to Infectious Mononucleosis

Response to Cortisone

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Although infectious mononucleosis is usually a relatively benign disease, complications sometimes occur. Skin eruption, hepatitis, splenic rupture, myocarditis, pulmonary infiltration, central nervous system involvement, hemolytic anemia, and thrombocytopenia have all been reported. Splenic rupture has probably been the most frequent fatal complication.

Thrombocytopenic purpura is one of the most uncommon complications, but due to the potential danger of cerebral and other hemorrhage and because of the favorable response to treatment it is important to recognize the condition early. In reported cases [1-6] with only symptomatic treatment thrombocytopenia persisted up to 14 days before spontaneous recovery. In the single reported case treated with adrenocorticotropin [7] recovery was much more rapid.

Adrenocorticotropin or cortisone has been used in toxic cases of infectious mononucleosis without thrombocytopenia [8-11] with good results. Typical response was disappearance of fever and increase in strength and appetite, all within 12 hours, and rapid diminution in size of liver and spleen. A case of Guillain-Barré syndrome complicating infectious mononucleosis also showed good response to adrenocorticotropin. In the hemolytic anemia cases [13] cortisone or adrenocorticotropin were apparently not used, but recovery occurred, although one patient out of five required splenectomy.

Our case is apparently the second one of thrombocytopenic purpura complicating infectious mononucleosis to be treated with cortisone.

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Report of Case

A 23-year-old white man, a dental student, employed part time by the hospital as an extern, developed generalized malaise about May 12, 1955. A day or so later he noticed weakness and occasional dizziness. On May 16, 1955, he began to bleed from his nose. Cauterization was necessary, but some oozing persisted. About the time of his nosebleed he noticed small purple spots scattered diffusely over his body. He had no joint pains, no nausea or vomiting. He passed tarry stools before admission to the hospital, but he attributed this to swallowing considerable blood. When oozing of blood continued from the nose, blood studies were done and a low platelet count found. He was admitted to the hospital on May 19, 1955.

His past history indicated no previous bleeding episodes. He had nosebleeds before, but always related to trauma. Tooth extractions and cuts had always healed without difficulty. He suffered a fractured skull at age 10, with no sequelae. There was no familial history of blood dyscrasias. He had served in the Navy from 1952 to 1954 and was in good health at that time. On March 4, 1955, slightly more than two months before onset of his present illness, a physical examination showed nothing abnormal and a complete blood cell count was entirely normal; blood smear showed adequate platelets.

Admission physical showed a pale young man appearing ill. He was well developed and well nourished. There were blood clots in both nostrils and small hemorrhagic areas on the hard and soft palate and posterior pharynx. His skin showed scattered purpuric spots on the trunk and all extremities. There was no lymphadenopathy. The liver was palpable 2 cm. below the right costal margin, and the edge was firm and not tender. A firm spleen was palpable 4 cm. belom the costal margin. The remainder of the complete physical examination was within normal limits.

A platelet count prior to admission was less than 10,000 per cubic millimeter. Total white blood cell count was 7500, with a neutropenia (34%) and a relative lymphocytosis with 13% of the cells interpreted as immature forms. Hemoglobin was 14 gm. per 100 cc., bleeding time was

15 minutes, and coagulation time, 5 minutes. Prothrombin activity was 100%.

Because of the rapid onset and the findings it was at first feared that the patient had acute leukemia. After examination of the patient the impression was infectious mononucleosis with thrombocytopenia. A sternal marrow preparation showed hyperactivity but no evidence of leukemia. Numerous megakaryocytes with unreleased platelets were seen. Hydrocortisone and very close observation of the patient were recommended. Positioning of the patient in a head-up position was done. Splenectomy was planned should the bleeding continue.

Hydrocortisone in doses of 40 mg. every six hours was started in the afternoon of the day of admission, May 19. Some oozing of blood from the nose continued the night of the 19th and during the day of the 20th. Platelet count on May 20 was 16,700, hematocrit was 41%, white blood cell count was 12,600, with 61% lymphocytes. Heterophile agglutination was negative. After May 20 there was no further evidence of bleeding. On May 21 platelet count was 58,000, and on May 23 it was 135,400. By May 23 the white blood cell count was 17,950 and showed cells typical of mononucleosis. On May 23 heterophile agglutination was positive 1:896 unabsorbed and 1:448 absorbed, and a Coomb's test was negative. Hydrocortisone was discontinued on May 24. The spleen and liver regressed in size, and the patient began to feel well. On May 25, however, he developed fever and sore throat. Exudate was present on the tonsils. Culture showed streptococci. This responded promptly to penicillin. Thereafter, the patient recovered uneventfully. He continued for the next two months to have symptoms of tiredness, but blood studies remained normal.

Comment

Thrombocytopenia can be due to at least five factors: deficient formation of platelets, inhibition of release of platelets from bone marrow, platelet thrombosis, circulating platelet agglutinins, and excessive destruction of platelets by the spleen. Probably the latter two—agglutinins and excessive destruction (hypersplenism)—are mostly responsible for the thrombocytopenia associated with infectious mononucleosis, but inhibition of release of platelets may be an added factor.

With thrombocytopenia due to any cause there is vascular wall permeability, impairment of vessel contractility after injury, and reduced clot retraction. Cortisone has been thought to reverse the vessel wall changes and to inhibit circulating agglutinins.[14] These effects may explain the rapid improvement in cases of thrombocytopenia similar to the one reported. In addition, the fever-reducing properties and nonspecific "tonic" effects were also evident.

Summary

A case of thrombocytopenia complicating infectious mononucleosis with favorable response to cortisone is reported. Though it is uncommon, the potential danger and the rapid response to treatment justify asking for increased awareness of this condition.

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REFERENCES

1. Berte, S. J.: Infectious Mononucleosis: A Review of the Literature, U. S. Armed Forces M. J. 5:1290-1299 (Sept.) 1954.

2. Green, L.: An Unusual Case of Infectious Mononucleosis, Canad. M. A. J. 72:36-37 (Jan. 1) 1955.

3. Linden, L.: Thrombocytopenic Purpura in Course of Infectious Mononucleosis, Nord. med. 49:643-645 (May 1) 1953.

4. Ogilvie, C. M., and Parry, T. E.: Infectious Mononucleosis with Thrombocytopenic Purpura, Brit. M. J. 2:977-979 (Nov. 1) 1952.

5. Smith, W. L.: Infectious Mononucleosis with Acute Thrombocytopenic Purpura: Report of Case, J. M. A. Alabama 22:257-260 (April) 1953.

6. Volpe, R.; Sparks, B. B., and Mautner, L. S.: Thrombocytopenic Purpura Complicating Infectious Mononucleosis, Canad. M. A. J. 68:269-272 (March) 1953.

7. Mateo de Acosta, O.: Púrpura trombopénica en mononucleosis infecciosa: Reporte de un caso, Arch. méd. Cuba 4:627-628 (Nov.) 1953.

8. Doran, J. K., and Weisberger, A. S.: The Use of ACTH in Infectious Mononucleosis, Ann. Int. Med. 38:1058-1062 (May) 1953.

9. Johnson, W. B.: Infectious Mononucleosis Treated with Cortisone, Missouri Med. 51:890-892 (Nov.) 1954.

10. Redmond, A. J.: Infectious Mononucleosis Treated with ACTH, New York J. Med. 54:3411-3414 (Dec. 15) 1954.

11. Saunders, R. H., Jr., and Adams, E.: Changes in Circulating Leukocytes Following Administration of Adrenal Cortical Extract (ACE) and Adrenocorticotropic Hormone (ACTH) in Infectious Mononucleosis and Chronic Lymphatic Leukemia, Blood 5:732-741 (Aug.) 1950.

12. Fiese, M. J.; Cheu, S., and Radding, J.: Guillian-Barré Syndrome in Infectious Mononucleosis: Report of Case with Recovery Following Administration of Cortisone, A. M. A. Arch. Int. Med. 92:438-441 (Sept.) 1953.

13. Samuels, M. L.: Hemolytic Anemia Complicating Infectious Mononucleosis: Report of 3 Cases, U. S. Armed Forces M. J. 4:1778-1782 (Dec.) 1953.

14. Stefanini, M.: Management of Thrombocytopenic States, A. M. A. Arch. Int. Med. 95:543-556 (April) 1955.

Emboli Arising in the Lungs

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Embolization from the systemic circulation to the lungs is a relatively common phenomenon. Reports of embolization from the lungs to the systemic circulation are rare. Spain and Moses[1] note that in a series of 5000 postmortem examinations systemic emboli resulting from pulmonary thrombophlebitis occurred in only one instance. A review of the literature revealed only one additional similar case.

Thrombi occur in the pulmonary veins less frequently than in the systemic veins because of the constant motion of the lungs, the protection against trauma offered by the bony chest cage, and the situation of the pulmonary veins at heart level, obviating the support of a long column of blood.

The purpose of this paper is to report a case in which emboli arising in the smaller veins of the pulmonary system spread to the arteries of the systemic system, causing profound symptoms and ultimately death. The source of the emboli was thought to be a pneumonic area of the lung.

Report of Case

A 23-year-old white man, was admitted to The New York Polyclinic Medical School and Hospital on Aug. 5, 1952, because of paralysis of the right upper and lower extremities and loss of speech of a few hours' duration. He died on Sept. 22, 1952, 48 days after admission.

He had been in his usual state of health until one week before admission, at which time he started to have malaise, cough, and high fever. A diagnosis of "virus infection" was made by the physician who treated him at home, and he was given penicillin and chlortetracycline (Aureomycin) without noticeable effect. On the morning of admission he suddenly developed paralysis of the right upper and lower extremities and loss of speech.

Past history revealed that he was subject to frequent sore throat until the age of 15 years, at which time a tonsillectomy was done. There was no history of rheumatic fever or scarlet fever. At the age of 16 years, during the course of a routine physical examination at school, he was told that he had a heart murmur and that he should "take things easy." He was first seen by one of us at the age of 18 years, at which time he complained of easy fatigability and shortness of breath on moderate exertion. Examination revealed a slightly enlarged heart, regular rhythm, presystolic murmur at the apex, and blood pressure 110/68. A diagnosis of chronic rheumatic heart disease was made. When next seen, in April, 1950, at age 21 years, shortness of breath had increased, and he was digitalized. He was last seen in the office on July 11, 1952. He complained of inability to walk more then two blocks because of shortness of breath. Examination revealed slight cyanosis of the lips. The heart was enlarged; the PMI being in the sixth interspace, 3 cm. to the left of the midclavicular line. A Grade 2 systolic murmur was heard at the apex. The pulmonic second sound was much louder than the aortic second sound. Fluoroscopy showed increase of the hilar shadows. The advisability of a mitral commissurotomy operation was suggested to the patient. One month later he was admitted to the hospital for the present illness.

Physical examination disclosed a well-developed, well-nourished, white man, acutely ill, dyspneic, orthopneic, and cyanotic. Temperature was 103.6 F; pulse, 92; respirations, 28, and blood pressure, 120/80. The skin was warm and moist. A careful search for petechiae revealed none. The pupils were equal and regular and reacted to light. The lips were pulled to the left. The tongue deviated to the right. No petechiae were seen on the conjunctivae or the mucous membrane of the mouth. The heart was enlarged to the left; the rhythm was regular, and the sounds, distant, and no murmurs were heard. There were dullness, diminished breath sounds, and crepitant rales over the lower half of the right lung field posteriorly. The abdomen was soft and without tenderness, masses, or palpable organs. There was a flaccid paralysis of the right upper and lower extremities. A positive plantar reflex was present on the right. Diagnoses of 1. chronic rheumatic heart disease, 2. cerebral embolus, and 3. possible subacute bacterial endocarditis were made.

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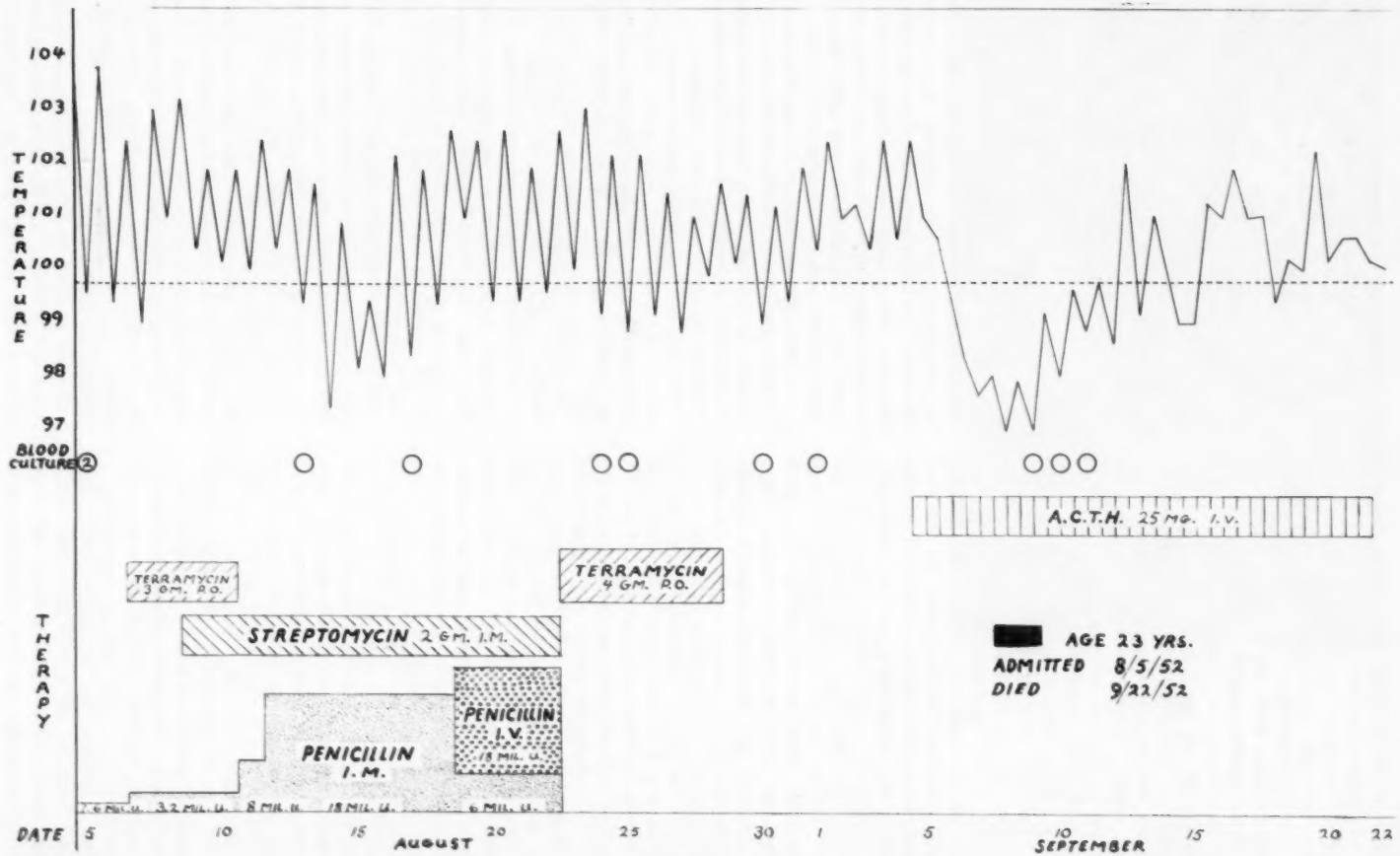
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DIED 9/22/52
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SEPTEMBER

Figure 1

Course in Hospital.—Because the diagnosis of subacute bacterial endocarditis was strongly suspected and because of the fear of further damage to the heart and additional embolic episodes he was started on antibiotic and anticoagulant therapy immediately after blood was drawn for culture. He was given aqueous penicillin, 200,000 units I. M., every three hours, and bishydroxycoumarin (Dicumarol), 200 mg. the first day and 50 mg. the second day. On the third day, although the prothrombin time was 35 seconds (control, 14), a second embolic episode occurred. The left leg and foot became cold and painful, and pulses in the dorsalis pedis, posterior tibial, popliteal, and femoral arteries were no longer palpable on that side. Penicillin was increased to 400,000 units I.M. every three hours and oxytetracycline (Terramycin), 0.5 gm. by mouth every four hours, was added. On the fourth day, although no additional bishydroxycoumarin had been given, the prothrombin time was over 60 seconds (control, 14). Vitamin K was given intravenously, and the prothrombin time returned to normal within 12 hours. On the fifth day the patient was still critically ill, and there were no changes in the abnormal findings in the lungs, heart, and extremities. Initial blood cultures and seven succeeding ones done during the course of the illness were reported negative. Streptomycin, 0.5 gm. every six hours, was added to the therapy. On the eighth day there was no change in the patient's condition. He continually complained of pain in the lower half of the right side of the chest and in the left leg and foot. A presystolic murmur at the apex was heard at this time. Oxytetracycline therapy was stopped and the penicillin increased to 1,000,000 units every three hours. At this time we still believed that we were dealing with subacute bacterial endocarditis. During the next few days the patient appeared to be somewhat improved in that temperatures were generally lower and toxicity less. This apparent improvement was transient, and on the 20th day the penicillin and streptomycin were stopped and oxytetracycline restarted. He received 4 gm. a day in divided doses by mouth for the next nine days without any apparent effect. At this time it occurred to us that we might be dealing with a case of acute rheumatic carditis and arteritis, and it was decided to try a course of corticotropin (ACTH) therapy. On the 33d day 25 mg. of corticotropin in 500 ml. of 5% dextrose in water was given I.V. over a period of eight hours. This was repeated every day for 16 days until his death. At first the response was dramatic, with a rapid fall of temperature to normal, a complete loss of toxicity, and a sense of well being. After a few days there was a gradual stepwise rise of temperature and return to his previous state. He died on the 49th hospital day. Throughout the course of his illness the findings of consolidation in the lower portion of the right side of the chest persisted. A chest x-ray taken during the first week after admission showed a diffuse density over the right lower lobe consistent with consolidation. The heart was markedly enlarged. Electrocardiogram was interpreted as indicative of right ventricular hypertrophy and strain.

Autopsy Observations.—Only the significant gross and microscopic findings will be mentioned.

The heart weighed 700 gm. There was hypertrophy and dilatation of both auricles and ventricles. The mitral valve presented a fish-mouth appearance. The coronary arteries were soft and collapsible throughout.

The aorta and large tributaries showed minimal arteriosclerotic changes. The left common iliac artery was occluded by a recent thrombus. The left innominate vein was occluded by a recent thrombus. The larger pulmonary arteries, primary, secondary, and tertiary branches, showed moderate to marked intimal sclerosis with eccentrically narrowed lumen, some of which were completely occluded by firm, adherent, grayish-red thrombi.

The lungs showed many recent and old infarcts. The pulmonary arteries in the infarcted area were occluded by old and recent thrombi. Elsewhere the pulmonary parenchyma showed alternate bronchopneumonic areas, edema, and congestion.

The right and left pleural cavities contained 100 ml. of red-tinged fluid, with easily separable, shaggy, reddish gray, friable adhesions. The peritoneal cavity contained 750 ml. of clear yellow fluid.

Microscopic Examination.—The mural endocardium of the left auricle was fibrotic. The myocardial fibers were hypertrophied. There was an increase in perivascular fibrous connective tissue. There were no Aschoff bodies. The coronary arteries were normal. The mitral and aortic valves showed no lesions characteristic of active rheumatic endocarditis.

Sections from the left innominate vein and left common iliac artery showed complete occlusion of their lumina by recent thrombi. The aorta and large tributaries did not show lesions typical of rheumatic aortitis or arteritis. Sections from the larger pulmonary arteries showed thickening of the intima by loose fibrillar connective tissue with fibroblasts and a variable number of small, in places large, mononuclear cells. In other areas there were intimal lipid deposits. Multiple sections from the grossly described thrombosed pulmonary arteries showed recent and older organizing thrombi, some with recanalization.

Multiple sections from the lungs showed many recent and old infarcts. The intervening parenchyma showed varying degrees of bronchopneu-

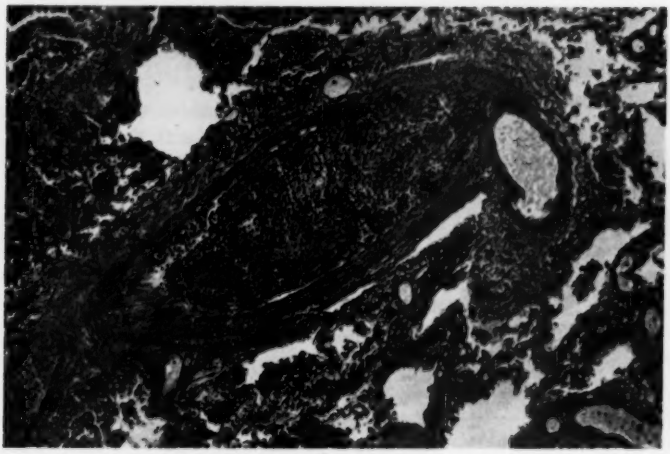

Fig. 2.—Thrombosis of medium-size vein in pneumonic area of lung.

monia. The intrapulmonary arterioles showed intimal proliferation with eccentrically narrowed lumen, and/or concentrically hypertrophied walls. Some of these were occluded by thrombi, most probably platelet thrombi. In areas, the adjacent venule was similarly occluded by thrombus.

The pleura was thickened by a fibrinous exudate with polynuclear and mononuclear cells in variable proportions.

Comment

The usual source of systemic emboli in rheumatic heart disease is the mural thrombi present in one or another chamber of the left heart. Many investigators in analyzing their series of such cases find this to be true, yet, in most instances there remains a variable percentage of cases in which no mural thrombi can be found to explain the source of these emboli. Several explanations have been offered to account for this. In some instances it is claimed that the mural thrombus is dislodged in its entirety to form the embolus and thereby leaves little or no evidence of its former presence in the heart. Occasionally a roughened area on the wall of one of the chambers is taken to be the source of an embolus. Calcific plaques on stenotic valves have been indicated as a source of emboli. Small verrucous vegetations (nonbacterial thrombotic endocarditis) frequently seen on the valves of the heart are suggested as being the source of many of these emboli. Finally, paradoxical embolus by way of a patent foramen ovale has been cited as the cause of peripheral infarction. This last example, while uncommon, is physiologically feasible in chronic rheumatic heart disease when pulmonary hypertension is present.

While systemic emboli may arise as a result of any of the foregoing causes, we believe that a hitherto infrequently suspected site of origin exists which might more easily explain the source of these emboli. This site of origin we believe to be the smaller veins of the lungs.

When the case presented here was autopsied, it was confidently expected that vegetations on the heart valves or endocardium would be found to explain the embolic phenomena which had occurred. Upon opening the heart we were chagrined to find only a smooth, glistening, unbroken endocardium. Vegetations, mural thrombi, or patent foramen ovale were not present. It was not until after a detailed examination of the lungs, including microscopic sections, was carried out that we became aware of the probable source of the emboli.

Thrombus in the vein of a lung as a source of systemic embolus has always been considered to be a relatively rare occurrence. Spain and Moses [1] comment on this observation but then go on to say that when (in a series of autopsies in which there were systemic infarcts for which there were

no intracardiac explanations) the pulmonary veins were carefully dissected, 15 cases were found in a relatively short time in which the source of the embolus was a thrombus in a pulmonary vein. The causes of pulmonary venous thromboses have been listed as pneumonia, pneumoconiosis, primary pulmonary venous sclerosis, tuberculosis, bronchiectasis, carcinoma, and pulmonary infarct. We believe that the cause of the pulmonary venous thromboses in our case was the refractory pneumonic process in the lower lobe of the right lung. Since there was no foramen ovale and no evidence of a thrombus past or present in the heart, we must conclude that the pulmonary venous thrombi were the site of origin of the emboli.

We feel that a more careful dissection and microscopic examination of the smaller pulmonary veins might shed some light on the site of origin of systemic emboli in those cases for which no intracardiac reason can be found.

Summary

A case of rheumatic heart disease is reported in which there was embolization to the systemic arteries and in which the site of origin of the emboli was thought to be the smaller veins of the lungs.

Many investigators in reporting the site of origin of systemic emboli in rheumatic heart disease find a variable number of cases for which no intracardiac source can be demonstrated.

The generally held belief, at present, that pulmonary veins are rarely the source of systemic emboli might have to be modified.

It is suggested that a more careful dissection of the smaller pulmonary veins in such cases might reveal the source of the emboli.

205 E. 69th St. (21) (Dr. Pomerantz).

REFERENCE

1. Spain, D. M., and Moses, J. B.: Thrombosis and Embolism of Pulmonary Vessels with Special Reference to Pulmonary Vein Thrombosis, Am. J. M. Sc. 212:707-712 (Dec.) 1946.

An Unusual Case of Wilson's Disease

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HEPATOLENTICULAR degeneration is a heredofamilial disorder characterized by degenerative changes in the lenticular nuclei, hepatic cirrhosis, and a pathognomonic deposition of greenish-brown pigment in Descemet's membrane at the limbus of the cornea, known as the Kayser-Fleischer ring. Recent investigation has revealed a defect in protein and copper metabolism in patients with this disease manifested by fluctuating amino-aciduria, elevated copper excretion, and normal or depressed serum copper levels.* Recognition of this disease is difficult because all too often it is simply not considered in the differential diagnosis. Frequently patients with Wilson's disease are obscured by being followed in large neurology outpatient clinics with various forms of Parkinsonism or as cases of juvenile cirrhosis of unknown etiology.

Since Kennear Wilson's classical monograph on "progressive lenticular degeneration,"[4] the finding of increased amounts of copper in the brain and liver of patients with this disease has stimulated great interest and investigative effort in tracing the etiology of this disease to what is thought to be a recessively transmitted metabolic defect. Genetic studies of families of patients with Wilson's disease have revealed an amazingly high incidence of consanguinity.[5] The evidence that the biochemical abnormalities are inherited in an autosomal recessive manner is very convincing. Accordingly parents of patients with this disease have not been found to be affected in any way or to exhibit any of the biochemical abnormalities of the disease.

Clinically this disease most commonly begins in the first or second decade of life, usually manifesting initial symptoms referable to the nervous system.[6] Evidence of hepatic impairment is usually latent, only becoming apparent if the patient lives long enough. Early signs are tremors of the extremities, incoordination, difficulty with articulation, dysphagia, hoarseness, ptyalism, and rigidity. The finding of Kayser-Fleischer rings is considered to be diagnostic. Frequently this characteristic can only be discerned with the aid of a slit lamp. Of considerable diagnostic importance also is the finding of a low serum copper associated with a high urinary copper excretion and amino-aciduria, the latter containing not only many amino acids found in normal urine, but also proline and citrulline, two amino acids not found in normal urine. Serum copper oxidase activity is consistently reduced, a fact that is correlated with reduced ceruloplasmin (copper-binding globulin) content of the serum.[4]

The present case is of unusual interest because of the manner in which he came to the attention of medical officers at a basic training camp and the difficulty with which the diagnosis was established, illustrating the importance of maintaining a high index of suspicion in order to make the diagnosis of this disease.

Report of a Case

A 19-year-old single white youth was admitted to the U. S. Army Hospital, Camp Chaffee, Ark., on Oct. 19, 1955, for psychiatric and neurological observation. He was in his fourth week of basic training when referred to the Mental Hygiene Consultation Service by his company commander because he appeared constantly in a daze, was unable to keep up with the rest of the troops, and apparently had great difficulty in grasping anything that was being taught. Because of a strikingly blank facial expression he was thought to be suffering from some form of psychiatric illness and was therefore first referred to the psychiatric service of the hospital. At that time he gave a history of the onset of weakness of both lower extremities beginning five months previously, May 1955.

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* References 1-3.

Throughout the summer months he became progressively weaker and slower in all his movements. In August, 1955, he noted constant drooling of saliva followed by difficulty in swallowing. His friends described his appearance as that of constant "sadness." He became so clumsy that he was of little use to his father on the farm. Because of the generalized slowness and clumsiness of movement he was no longer able to enjoy dancing. To his friends he appeared to be losing all interest in life. After being inducted in September he noted that his speech became difficult to understand. In his basic training he repeatedly had to drop out of rank during marching, was too poorly coordinated to qualify on the M-1 range, and was finally sent to the Mental Hygiene Consultation Service for disposition. Past medical history was noncontributory. An older brother had died at age 18 of "cancer of the liver." Another brother age 12 and two sisters ages 22 and 15 are all living and well, as are the father and mother. No history of a similar illness in other members of the family could be obtained. The patient had been a star football player during his high school career. Physical examination revealed a well developed, muscular, chronically ill demented-appearing young man. Blood pressure was 126/76 and pulse, 82. A fixed facial expression was the most striking feature. Volitional control of facial musculature was retained, but the movements were slow and weak. Provoking laughter resulted in a fixed exaggerated smile. Slight asymmetrical ptosis of the lids in addition to the extremely poorly articulated speech and ptyalism were noted. Generalized bradykinesia and loss of associated movements on walking were prominent. The cranial nerves were all intact but for definite motor weakness of the muscles supplied by the 5th, 7th, 9th, 10th, and 12th nerves. The deep tendon reflexes were all intact. No pathological reflexes were elicited. The sensory examination was completely normal. The characteristic pill-rolling tremor, cogwheel rigidity, and festinating gait were not present. There was no increase of weakness on repetitive movements. The liver and spleen were not enlarged.

Laboratory testing revealed normal urine, serology, and spinal fluid. Hemogram was normal but for a slight leukopenia of 4900 WBC, with a normal differential. Sulfobromophthalein (Bromsulphthalein), alkaline phosphatase, prothrombin time, serum bilirubin, and thymol turbidity were all within normal limits. The cephalin cholesterol flocculation was repeatedly abnormal, with a 4+ reaction. Serum proteins revealed an albumin of 2.5 gm. per 100 cc. and a globulin of 2.9 gm. per 100 cc. Special studies of copper metabolism revealed a serum copper of 117.9 γ per 100 cc. (normal, 200-260 γ per 100 cc.), urinary copper 187.8 γ per 24 hours (normal, 35 γ per liter), with a total 24-hour volume of 1240 ml. Urine amino acid output was 664 mg. per 24 hours (normal, 150-200 mg/24 hours). Skull and cervical spine films were negative except for an incidental finding of a congenital abnormality of the odontoid process. Barium swallow to delineate the deglutition mechanism was considered normal. Psychological testing, including the Wechsler-Bellevue, Draw-a-Person, Sentence completion, Bender-Gestalt, and Color-Form-Sorting tests, revealed a full-scale I. Q. of 86 with definite indications of organicity (round, hollow drawings, "stickiness" in shifting, and perseveration.) Other studies at a different hospital† revealed a serum copper of 120 γ per 100 cc. (normal values by this lab 68 to 134 γ per 100 cc.), serum mucoprotein of 10 mg. per 100 cc. (normal, 10-13 mg. per 100 cc.), serum iron of 63 γ per 100 cc. (normal, 70-170 γ per 100 cc.), and urine copper of 370 γ per liter (normal, 120 γ per liter). Electrophoretic pattern of serum showed the γ-globulin at the top edge of normal, but it was otherwise normal. Liver biopsy revealed normal-appearing hepatic tissue. Bone marrow examination revealed slightly hyperplastic red cell series, with some slight left shift which was considered not significantly abnormal. Urinary coproporphyrins were slightly above normal.

Because of the striking bulbar signs, especially the ptosis, the diagnosis of myasthenia gravis was strongly considered initially. Repeated intravenous edrophonium tests[7] were considered to be within normal limits. Other diagnoses considered were schizophrenic reaction, catatonic type, multiple sclerosis, pseudobulbar palsy, postencephalitic Parkinsonism, and amyotrophic lateral sclerosis. When these diagnoses were each ruled out, the possibility of hepatolenticular degeneration was considered. With careful observation a narrow band of greenish-brown pigment 2 mm. wide could be seen at the limbus of the cornea. A slit-lamp examination was obtained and confirmed this finding.

After prolonged observation the only objective sign of progression of the disease was the development of an uncontrollable tremor of the right hand with resulting difficulty in eating. Trihexyphenidyl (Artane), 2.0 mg. t. i. d., proved of great benefit in controlling the ptyalism. Belladonna tincture was of less benefit. It was felt that this patient deserved a trial of dimercaprol (BAL) therapy according to the method of Denny-Brown.[8] On Nov. 30, 1955, he was started on dimercaprol therapy, 1.5 cc. deep I. M. twice daily for an anticipated course of 12 days of treatment. After four days of treatment anorexia and lethargy developed. His movements became slower and

† With permission of Dr. Harold V. Cummins, Ochsner Clinic, New Orleans.

slower. By the eighth day of treatment nausea and vomiting curtailed any food or fluid intake, and he became too weak to get out of bed. Urinalysis revealed albuminuria and hematuria. Blood N. P. N. rose to a maximum of 54.3 mg. per 100 cc. His blood pressure became persistently elevated to a maximum of 150/110. Urinary output declined to 400 cc. Treatment was stopped after the eighth day, and intravenous fluids were administered. Following the relief of the dehydration, urinary output rose to a level of over 1000 cc. daily. Over the next 48 hours the nausea, vomiting, and severe lethargy gradually disappeared. Approximately five days after stopping treatment the patient appeared to have regained his pretreatment level. Over the next two weeks the only objective sign of improvement was the disappearance of the hand tremor. The blood N. P. N. gradually returned to normal, as did the urinary abnormalities. No change in the appearance of the Kayser-Fleischer rings was noted. It was the opinion of most observers that the azotemia and urinary abnormalities were the result of a prerenal mechanism (dehydration) rather than toxic effects of dimercaprol on the kidneys.

Comment

This case presented an interesting diagnostic problem, which was finally solved when the presence of a narrow zone of pericorneal pigmentation was noted and confirmed by slit-lamp examination. The existence of a Parkinsonian syndrome without a history of childhood encephalitis led to closer scrutiny of the cornea. The negative family history obtained initially must be qualified by information obtained from subsequent observers, who have found strong reason to suspect that 10 to 12 members of the immediate family have been affected by the disease.‡ In retrospect it is apparent that this patient has followed quite a typical pattern for patients with this disease. The presence of pseudobulbar signs and intellectual impairment, as exists in this case, is said to be a bad prognostic sign, indicative of cavitation in the lenticular nuclei and a more rapidly progressive form of the disease.[8] The cause of intensification of symptoms during the course of dimercaprol treatment is not known, but it is conceivable that rapid mobilization of copper from the lenticular nuclei could result in such a reaction. All the typical laboratory findings were present in this case: low serum copper, elevated urinary copper, abnormal amino-aciduria, and normal liver function tests except for a 4+ cephalin cholesterol flocculation.[9]

The course of this disease is variable, characterized by steady progression with increasing rigidity, tremors, dysphagia, loss of speech, mental deterioration, incontinence, and death, or in some cases by advancement of the disease in a series of exacerbations.[6] The possibility of utilizing various chelating agents in the treatment of this disease, such as dimercaprol and ethylenediamine tetraacetic acid (EDTA and Versene), has stimulated great interest in attempting to alter the inexorable course as described above. As a rule, death occurs in 2 to 5 years, with extremes of 5 weeks to 11 or more years having been reported. Marked relief of the incapacitating tremors, rigidity, and incoordination usually follows a course of dimercaprol treatment, which may be given in monthly intervals. The use of this agent in this case was in a comparatively early stage of the disease, before the onset of severe tremors and incoordination. The possible benefits of early treatment in this case as far as prolongation of life is concerned remains to be seen.

The mode of action of the chelating agents in this disease deserves further comment. Because of the deficiency of the copper-binding globulin, ceruloplasmin, it is felt that copper is transported in the serum in an "unattached" fashion, free to become bound to proteins of the tissue.§ Why selective sites such as the lenticular nuclei and liver are chosen is not known. An excess of copper then becomes deposited in these tissues. Because it is not firmly bound in the brain and liver, the copper readily forms soluble diffusible complexes with the amino acids of the blood, which are then easily excreted, thus the constant

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§ References 1 and 5.

correlation of the abnormal amino-aciduria with the elevated urinary copper excretion. Injection of a chelating agent results in further release of the loosely bound copper in the form of copper-chelating agent complexes and augmentation of the urinary excretion of copper. Apparently the copper is more firmly bound to the proteins of the liver than the brain, since no change in copper content of the liver occurs after treatment. Further discoveries remain to be made to explain adequately the hepatic cirrhosis which appears at varying stages of the disease.

Summary

Hepatolenticular degeneration is a fatal heredofamilial disease which usually begins in the first or second decade of life and progresses steadily or by exacerbations with tremors of the extremities, various bulbar signs and symptoms, and varying degrees of the Parkinsonian syndrome. The finding of Kayser-Fleischer rings differentiates this from other causes of Parkinsonism.

The case reported, discovered in a basic training camp, exhibiting a classical history and physical findings, proved a problem in diagnosis because of the psychiatric features and delay in careful examination for Kayser-Fleischer rings. Subsequent detailed laboratory studies confirmed the characteristic biochemical abnormalities of the disease.

A description of a course of dimercaprol (BAL) treatment in the present case is included to illustrate some of the problems involved in this treatment as well as the benefits derived. The rationale for the use of the chelating agents as well as the postulated underlying genetic and biochemical defects are summarized.

The importance of maintaining a high index of suspicion in order to recognize this disease is stressed.

Lieut. Col. Euclid G. Herndon Jr. gave suggestions in the preparation of this report.

REFERENCES

1. Earl, C. J.; Moulton, M. J., and Selverstone, B.: Metabolism of Copper in Wilson's Disease and in Normal Subjects: Studies with Cu-64, Am. J. Med. 17:205-213, 1954.

2. Brick, I. B.; Medical Progress: The Clinical Significance of Aminoaciduria, New England J. Med. 247:635-644, 1952.

3. Markowitz, H.; Gubler, C. J.; Mahoney, J. P.; Cartwright, G. E., and Wintrobe, M. M.: Studies on Copper Metabolism: XIV. Copper, Ceruloplasmin and Oxidase Activity in Sera of Normal Human Subjects, Pregnant Women, and Patients with Infection, Hepatolenticular Degeneration and the Nephrotic Syndrome, J. Clin. Invest. 34:1498-1508, 1955.

4. Wilson, S. A. K.: Progressive Lenticular Degeneration: A Familial Nervous Disease Associated with Cirrhosis of the Liver, Brain, 34:295-509, 1912.

5. Bearn, A. G.: Genetic and Biochemical Aspects of Wilson's Disease, Am. J. Med. 15:442-449, 1953.

6. Ford, F. R.: Diseases of the Nervous System in Infancy, Childhood and Adolescence, Ed. 3, Springfield, Ill., Charles C Thomas, Publisher, 1952

7. Osserman, K. E., and Teng, P.: Studies in Myasthenia Gravis—A Rapid Diagnostic Test: Further Progress with Edrophonium (Tensilon) Chloride, J. A. M. A. 160:153-155, 1956.

8. Denny-Brown, D., and Porter, H.: The Effect of BAL (2,3-Dimercaptopropanol) on Hepatolenticular Degeneration (Wilson's Disease), New England J. Med. 245:917-925, 1951.

9. Franklin, E. C., and Bauman, A.: Liver Dysfunction in Hepatolenticular Degeneration: Review of 11 Cases, Am. J. Med. 15:450-458, 1953.

Myasthenia Gravis Developing Fifteen Months After Removal of Thymoma

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A relationship between the thymus and myasthenia gravis has been accepted by a number of investigators.* However, the nature of this association is still unknown. Nevertheless, in patients with myasthenia gravis whose disease cannot be adequately controlled with medication, irradiation or removal of the thymus has been recommended.† The results of surgery have been variable, but it is generally agreed that they are better in those patients who have a simple hyperplasia of the thymus than in those with a thymic tumor.

The appearance of myasthenia gravis after the removal of a thymoma is quite rare. A review of the literature has disclosed only four cases in which symptoms of myasthenia developed following excision of a thymoma.

Fershtand and Shaw [14] reported the onset of myasthenia gravis in a 27-year-old man who had a three-week history of chest pain and signs of superior vena caval obstruction. A mass extending along the border of the right side of the heart was seen on the roentgenogram. At operation a thymic tumor was found, most of which was excised. Following the operation the patient became markedly prostrated. He responded to neostigmine (Prostigmin) with a complete remission of the myasthenia. However, he developed difficulty in breathing 15 months later, due to increased mediastinal pressure, and died. At autopsy a malignant thymoma was found invading the mediastinal structures, including the heart. A second case was described by Fisher and Child.[15] Their patient was admitted to the hospital with a history of severe orthopnea and ankle edema of four weeks' duration. Four years previously he had had a cough with occasional blood-tinged expectoration. When he sought medical advice 18 months after the onset of the cough, a mediastinal mass was seen on roentgenography of the chest which was thought to be either a neoplasm or an aortic aneurysm. Examination at that time showed the mass to have increased in size with the addition of a right pleural effusion. A large thymoma was removed from the anterior mediastinum, but there were implants in the right thoracic cavity. The tumor was considered to be malignant in spite of the benign histologic appearance. On closing the chest there was noted severe difficulty in breathing. The patient was given 1 mg. of neostigmine with marked improvement. Neostigmine was administered postoperatively. He was well for four days, when he suddenly developed respiratory distress and died. There were no signs or symptoms of myasthenia prior to the operation. Rowland and co-workers [16] mentioned two patients in their series in whom myasthenia gravis developed after removal of thymomas. In the first, the myasthenia gravis appeared five years after excision of the thymoma; the patient succumbed to the disease. In the second patient, the myasthenia was noted a few weeks after the operation; hyperplastic thymic remnants were found at autopsy.

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From the Neuropsychiatric (Dr. Madonick and Dr. Karliner), Thoracic Surgical (Dr. Rubin), and Medical (Dr. Levine) Services, The Morrisania City Hospital.

* References 1-5.

† References 6-13.

We are reporting a case of myasthenia gravis occurring in a patient 15 months after removal of a thymoma. At the time of the operation the patient had no symptoms of the disease. At a second operation, an exploration of the anterior mediastinum was done, and residual thymic tissue was found and excised.

Report of Case

A 33-year-old Negro woman was admitted to the Morrisania City Hospital on March 30, 1953, from the Diagnostic Clinic, with a history of the finding of a mediastinal shadow on a routine chest roentgenogram. There were no complaints; the patient was enjoying good health. On radiographic examination of the chest a round area of increased density adjacent to the upper portion of the left cardiac border was noted. This mass was in the anterior mediastinum (Fig. 1). The mass was thought to be thymic in origin. On April 10, 1953, under general anesthesia, the left pleural cavity was entered through a left lateral incision. There were no pathologic findings in the left lung or pleural cavity. A hard, lobulated, yellow mass was found in the anterior mediastinum, occupying the so-called thymic area at the base of the great vessels. It was easily enucleated.

The tumor was a well-encapsulated, roughly triangular, nodular mass, measuring 6×4×3 cm. and weighing 15 gm. (Fig. 2*A* and *B*). It was firm and somewhat rubbery in consistency. On cut section well-circumscribed nodules of varying size were seen which were separated and surrounded by bands of fibrous tissue. The nodules were pinkish-grey in color, with a fine granular appearance. On microscopic examination the lobules consisted of cells resembling reticulum cells. There was no invasion of the fibrous capsule. The cells were closely packed and uniform in size. The cell borders were indistinct and the cytoplasm, scant. The nuclei were fairly large and vesicular, with prominent nucleoli. Mitotic figures were fairly numerous. A diffuse sprinkling with lymphocytes was present. Hassall's corpuscles could not be identified. The histologic diagnosis was thymoma (Fig. 3).

The patient was well after operation and carried out all her household and other duties without difficulty. In the summer of 1954 she complained of double vision and weakness of the arms and legs. She was readmitted to the hospital on Dec. 17, 1954, with complaints of weakness of the arms and legs, inability to elevate the lids, and occasional hoarseness. These difficulties were intermittent, lasting for a few hours. Recently she

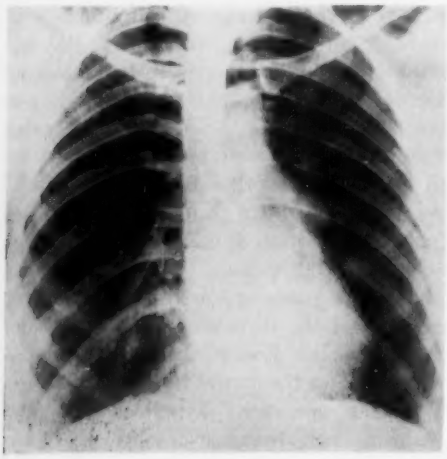


Fig. 1.—Conventional x-ray of chest, showing rounded mass in the left mediastinum just above the heart.

Fig. 2.—Well-encapsulated thymoma which, on cut section, contains numerous lobules separated by dense connective tissue.

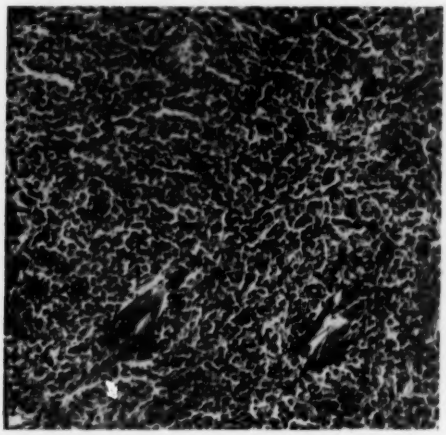


Fig. 3.—Microscopic section of the thymoma. The tumor consists of well-defined lobules of large, reticular cells with large vesicular nuclei.

also noted that she had to take much fluid with her food in order to be able to swallow it. On examination slight bilateral ptosis was observed. Since the complaints could not be demonstrated objectively, a quinine test was performed.[17] About one and one-half hours after 10 grains (0.6 gm.) of quinine was administered by mouth, the patient suddenly became extremely weak. Her voice became low, and she was dysarthric. The upper lids drooped completely. There was marked weakness in both wrists, but there were no reflex or sensory changes. She was given 0.5 mg. of neostigmine intravenously and a second dose 10 minutes later with 1/150 grain (0.4 mg.) of atropine. In 10 minutes there was a complete return of power; the ptosis had disappeared.

On blood cell count there were 6,100 leukocytes, with a normal differential; the hemoglobin was 13.6 gms. per 100 cc. The blood potassium was 4.2 mg.; sodium, 141 mg.; calcium, 9.0 mg.; chlorides, 103 mg.; nonprotein nitrogen, 10 mg.; glucose, 82 mg.; cholesterol, 230 mg., and cholesterol esters, 117 mg. per 100 cc., respectively. The electrocardiogram was normal. On roentgenographic examination of the chest no mediastinal or pulmonary abnormalities were observed.

She was discharged from the hospital on Jan. 18, 1955, on therapy of oral neostigmine, 10 mg. three times daily. At home she had periods in which she complained of weakness in the limbs and double vision. Deep x-ray therapy, 2100 r, was given to the anterior and posterior mediastinum from Feb. 21 to April 14, 1955, without any improvement.

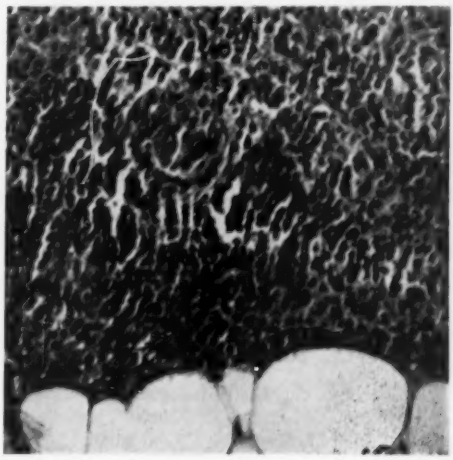
In view of the possibility of the presence of residual thymic tissue in the anterior mediastinum, the patient was readmitted to the hospital on May 3, 1955, for exploration of this area. Neostigmine was increased prior to operation to 20 mg. three times daily. On May 6, 1955, a vertical midline incision was made from 1 in. (2.5 cm.) above the upper border of the sternum to the xiphoid. The sternum was split longitudinally, and the mediastinal structures were explored. No tumor could be identified. However, a mass of grayish, fatty tissue measuring 6×2×0.25 cm. was encountered and excised. Microscopic examination of the specimen showed it to consist of islands of lymphoid tissue scattered throughout fatty tissue, with clearer areas resembling the medullary portion of the thymus. A structure resembling a Hassall's corpuscle was noted. The pathologic diagnosis was thymic tissue (Fig. 4).

The postoperative course was uneventful. At the time of discharge from the hospital she was taking neostigmine, 20 mg. three times daily. She was able to conduct her housework and had no complaints. On Sept. 19, 1955, the neostigmine was reduced to 10 mg. three times daily. The patient continued doing well. Neostigmine was discontinued on Oct. 17, 1955. She was well until Nov. 10, 1955, when she began to complain again of drooping of the eyelids and double vision. Neostigmine, 10 mg. three times daily, was resumed, with disappearance of symptoms. She is being maintained on this dosage at present.

Comment

The appearance of symptoms of myasthenia gravis 15 months after the excision of a benign thymoma in this patient prompted us to consider the possibility of residual thymic tissue in the anterior mediastinum,

Fig. 4.—Microscopic appearance of residual thymic tissue, showing a Hassall's corpuscle.



a region not visualized at the initial operation. There was no radiographic evidence to warrant the diagnosis of recurrence of the thymoma. The association of thymic hyperplasia, which may not be detected radiographically in patients with myasthenia gravis, has been noted by others. Blalock and co-workers [18] and Carson [19] emphasized that the clinical and radiologic examination for thymic enlargement was not always reliable. Thus Blalock and co-workers [18] carried out exploratory anterior mediastinotomies in six cases of myasthenia gravis. There was no roentgenographic evidence of a mediastinal tumor in any of the cases. Definite hyperplasia was demonstrated in five of the cases at operation. Hardyman and Bradshaw [20] reported three cases of myasthenia gravis in which an anterior mediastinotomy was done, in one, hyperplasia of the thymus was present. According to Schridde,[21] no microscopically recognizable thymic tissue should be present in people over 30 years of age. In a series of 32 patients, reported by Clagett and Eaton,[22] with myasthenia gravis on whom operation on the thymus was performed, a tumor was present in 15. They advocated thymic exploration in all cases of severe or progressive myasthenia gravis in which the patient's condition permitted surgery.

Summary

A 33-year-old woman developed myasthenia gravis 15 months following removal of an asymptomatic thymoma discovered on routine chest roentgenography. In view of the possible presence of thymic tissue elsewhere in the chest cavity or neck, exploration of the anterior mediastinum was done. The tissue removed from the mediastinum had the histologic appearance of thymus. Removal of the persistent thymus did not result in amelioration of symptoms in this case.

REFERENCES

1. Weigert, C.: II. Pathologisch-anatomischer Beitrag zur Erbschen Krankheit (Myasthenia gravis), Neurol. Centralbl. 20:597, 1901.

2. Bell, E. T.: Tumors of the Thymus in Myasthenia Gravis, J. Nerv. & Ment. Dis. 45:130, 1917.

3. Norris, E. H.: The Thymoma and Thymic Hyperplasia in Myasthenia Gravis, with Observations on the General Pathology, Am. J. Cancer 27:421, 1936.

4. Miller, H. G.: Myasthenia Gravis and the Thymus Gland, Arch. Path. 29:212, 1940.

5. Harvey, A. M.: Some Preliminary Observations on the Clinical Course of Myasthenia Gravis Before and After Thymectomy, Bull. New York Acad. Med. 24:505, 1948.

6. Poer, D. H.: Effect of Removal of Malignant Thymic Tumor in Case of Myasthenia Gravis, Ann. Surg. 115:586, 1942.

7. Blalock, A.: Thymectomy in the Treatment of Myasthenia Gravis: Report of 20 Cases, J. Thoracic Surg. 13:316, 1944.

8. Eaton, L. M., and Clagett, O. T.: Thymectomy in the Treatment of Myasthenia Gravis: Results in 72 Cases Compared with 142 Control Cases, J. A. M. A. 142:936, 1950.

9. Keynes, G.: The Surgery of the Thymus Gland (Hunterian Lecture), Brit. J. Surg. 33:201, 1946.

10. Keynes, G.: The Results of Thymectomy in Myasthenia Gravis, Brit. M. J. 2:611, 1949.

11. Viets, H. R.: Thymectomy in Myasthenia Gravis, Brit. M. J. 1:139, 1950.

12. Ross, R. T.: Thymectomy in the Treatment of Myasthenia Gravis, Lancet 1:785, 1952.

13. Eaton, L. M., and Clagett, O. T.: Present Status of Thymectomy in Treatment of Myasthenia Gravis, Am. J. Med. 19:703, 1955.

14. Fershtand, J. B., and Shaw, R. B.: Malignant Tumor of the Thymus Gland, Myasthenia Gravis Developing After Removal, Ann. Int. Med. 34:1025, 1951.

15. Fisher, J. H., and Child, C. G., III: Myasthenia Gravis Developing Acutely After Partial Removal of a Thymoma, New England J. Med. 252:891, 1955.

16. Rowland, L. P.; Hoefer, P. F. A.; Aranow, H., Jr., and Merritt, H. H.: Fatalities in Myasthenia Gravis: A Review of 39 Cases with 26 Autopsies, Neurology 6:307, 1956.

17. Harvey, A. M., and Whitehill, M. R.: Quinine as an Adjuvant to Prostigmine in the Diagnosis of Myasthenia Gravis, Bull. Johns Hopkins Hosp. 61:216, 1937.

18. Blalock, A.; Harvey, A. McG.; Ford, F. R., and Lilienthal, J. L., Jr.: The Treatment of

Myasthenia Gravis by Removal of the Thymus Gland: Preliminary Report, J. A. M. A. 117:1529, 1941.

19. Carson, J.: Discussion of Myasthenia Gravis and Thymectomy, Proc. Roy. Soc. Med. 36:140, 1942.

20. Hardyman, P. B., and Bradshaw, H. H.: Exploratory Anterior Mediastinotomy in 3 Cases of Myasthenia Gravis, Surg. Gynec. & Obst. 78:402, 1944.

21. Schridde, H., in Pathologische Anatomie, edited by L. Aschoff, Ed. 3, Jena, G. Fischer, 1913, Vol. 2, p. 173.

22. Clagett, O. T., and Eaton, L. M.: Surgical Treatment of Myasthenia Gravis, J. Thoracic Surg. 16:62, 1947.

Books

EDITED BY WILLIAM B. BEAN, M.D.

BOOK REVIEWS

Dictionary of Dietetics. By Rhoda Ellis. Price, $6. Pp. 152. Philosophical Library, Inc., 15 E. 40th St., New York 16, 1956.

The Dictionary of Dietetics is one of a series of fifty-three dictionaries and encyclopedias in the "Midcentury Library." The stated purpose is to define terms which will help the lay and professional person to understand the feeding problems of people in all stages of health and disease. The book would be more useful to physicians and dietitians if it had been written for professional people only. More exact and complete definitions of nutrition and diet-therapy terms could well replace most of the information on such food subjects as soups and desserts.

The book includes tables of caloric values, taken from the authoritative U. S. Department of Agriculture Handbook No. 8, under the definitions of many of the food groups.

ELIZABETH H. TUFT

Histopathologie du foie. By P. Cazal. Price, paper, 4000 fr., cloth, 4800 fr. Pp. 208, with 213 black-and-white and 24 color illustrations. Masson & Cie, 120 boulevard Saint-Germain, Paris, 6e, 1955.

This volume, written entirely in French, presents in atlas form the histopathology of the more important hepatic diseases. Most of the specimens were obtained by needle biopsy of the liver.

The photomicrographs are chiefly black and white, with, however, two color plates providing twenty-four illustrations. The selection of material, photomicrographic fields, photographic technique, and reproduction of the photomicrographs are excellent. In addition, many of the photomicrographs are accompanied by a schematic diagram indicating the important features of the corresponding illustration.

The text is brief but adequate and clearly presented. The author's technique for needle biopsy of the liver and histologic preparation of the tissue is included in an appendix. Throughout the volume the references are ample and include many publications in the English as well as the foreign literature.

The beautiful illustrations make this text an excellent and unique work. The captions accompanying the illustrations are easy to interpret even for a person who is not exceptionally fluent in the French language, and this should make this book a valuable addition to the library of any physician interested in the histopathology of diseases of the liver.

FRANCIS J. TENCZAN JR. M.D.

Advances in Internal Medicine. Volume VIII. Edited by William Dock and I. Snapper. Price, $9. Pp. 366, with 23 illustrations. The Year Book Publishers, Inc., 200 E. Illinois St., Chicago 11, 1956.

In this, the eighth volume of "Advances in Internal Medicine," Dock and Snapper have kept up the high standard of articles set in previous years. While there is no evident rhyme or reason for the selection of subjects, each is a unit in itself, and all are of interest and importance. Outstanding in the present volume are the authoritative and much-needed reviews on "Aldosterone," by Leutscher, and on "Hemoglobins and Disease," by Watson, although all the articles are of interest and documented with thorough bibliographies.

ARTHUR L. BLOOMFIELD, M.D.

Medical Students and Medical Sciences. By David Sinclair, M.D. Price, $5.75; 25s. Pp. 154. Oxford University Press, Amen House, Warwick Sq., London, E. C. 4; 114 Fifth Ave., New York 11, 1954.

David Sinclair, M.A., M.D., is an anatomist working with the tutorial system at Oxford, England. He is unquestionably a teacher, whether we judge by his book, his publications on such matters as essay type examinations, or the fact that he was once

sent on tour of some of the medical schools in this country to see what went on. He is also a man of substance, for he is about to leave the hallowed halls of Oxford, where stability would seem assured, if anywhere, for the unlaid bricks of Perth, Australia, where opportunity is certainly much greater than stability.

"Medical Students and Medical Sciences" gives observations backed by genuine interest and zeal in medical teaching rather than the claims of a man who presumes to have found the answers. There is no pretense, no tendency to defend any thesis ardently. A discursive book, Sinclair divides his fourteen chapters into four sections which consider students, teaching, the subject taught, and educational experiments. This is certainly a healthy bit of realism, often missing in educational discussion. Educationists to the contrary notwithstanding, matters of education are and must remain secondary to the primary task, amalgamation of students, teachers, and subjects. This Sinclair not only appreciates but feels intuitively.

It would be unfair to speak of a basic philosophy underlying Sinclair's presentation. The purpose of a review is to get someone to look at a book, not to provide an artificial digest which permits exploitation without representation. There is a basic philosophy, but it is in afluid state, open to discussion. It says that the elements are students and teachers and the container is the subject. The outlook is broad enough so that the restriction to medical students and sciences is unduly modest; any teacher in any field would find much of interest.

There are familiar topics, like the examination paper, selecting students, and curricula. Instead of bogging down in these topics, the discussions are refreshing, for one reason because widely different methods and backgrounds in England and America seem to flow together so often in uniform problems. Sources of minor quibble are rare and undisturbing. Direct rather than profound, provocative rather than authoritative, the book is a stimulant to reflection rather than a stuffy bit for an already pompous literature on the subject. Sinclair's last page cites Samuel Butler: "Life is the art of drawing sufficient conclusions from insufficient premises."

MAX MARSHALL.

Handbook of Poisons. By Robert H. Dreisbach, M.D., Ph.D. Price, $3. Pp. 426, with 18 figures, 19 pictures of artificial resusitators, and many chemical formulae. Lange Medical Publications, P. O. Box 1215, Los Altos, Calif., 1955.

This handbook treats the subject of clinical poisoning by considering industrial, household, medicinal, and natural hazards sources. The individual poisons are covered by description of the clinical findings, treatment of acute poisoning, prophylaxis, and prognosis. In most cases chemical formulae are included in the description of the drug or poison. The general index includes proprietary names as well as chemical names of the various poisons and medicinals. There are few references, and the author has sacrificed this information to provide a very complete summary of the diagnosis and treatment of the clinically important poisons. This book should prove a welcome addition to any general practitioner's book shelf.

ALEXANDER C. KEYL.

Histamine. Ciba Foundation Symposium Jointly with the Physiological Society and the British Pharmacological Society in Honor of Sir Henry Dale. Edited by G. E. W. Wolstenholme, O.B.E., M.A., M.B., B.Ch., Cecilia M. O'Connor, B.Sc., and many contributors. Price, $9. Pp. 472, with 133 illustrations. Little, Brown & Company, 34 Beacon St., Boston 6, 1956.

This is the record of two successive symposia held in London, the first a well-attended meeting sponsored by the two learned societies and the second a small conference at Ciba Foundation House. There is therefore some inequality of style and some unavoidable overlap in the record. Thus, the last section of the societies' meeting dealt with the "origin and significance of histamine in the body" and the first section of the Ciba symposium with the "origin and fate of histamine in the body." Still, repetition is the mother of studies and is no more than a minor defect in a volume which uncovers some of the broad vistas of the known and unknown properties of this nearly ubiquitious substance.

Those who read for general information will discover many interesting aspects of the problem, such as the large difference between endogenous and exogenous histamine,

the probability that histamine exists intracellularly in mast cells, in association with heparin and serotonin, and the consequent possibilities of mutual interaction of these substances in normal and abnormal vascular function. It seems from the discussion that the extraordinarily heterogenous group of substances called "histamine-liberators" have mostly in common a dispersing action on mast cells and that there is still room for argument on the specificity and significance of histaminase.

The volume is invaluable to investigators in such fields as vascular physiology and allergy and will be stimulating and informing to those who practice in these fields. For many others, students and practitioners, it is essentially a compact, well-edited reference source to who's who and what's new in histamine circles.

A. C. CORCORAN, M.D.

Cardiac Pressures and Pulses. By Aldo A. Luisada, M.D., and Chi Kong Liu, M.D. Price, $6. Pp. 116, with 51 charts and 5 tables. Grune & Stratton, Inc., 381 Fourth Ave., New York 16, 1956.

This small book by Luisada and Liu summarizes in 109 pages aspects of hemodynamic cardiac phenomena obtained by cardiac catheterization with the Fick principle for recording variations in cardiac output and pressure. The monograph includes a discussion, in more or less conventional fashion, of the cardiac cycle, technique of catheterization, normal patterns of pressure in the chambers and large vessels, abnormal pressure patterns, artifacts, and formulas used in cardiac catheterization. There is a bibliography of 77 references and an index.

There is nothing really unique about the monograph or anything new. It contains the ideas and methods of approach and thinking of Luisada and his associates, which have been published already. This book does accumulate them however, so that it can serve as a source of this information for others. The monograph will serve beginners best, provided they realize it is a condensed version of the problem and the authors' points of view. The illustrations are numerous and clearly presented, with the time along the abscissa of the illustrations drawn by fast-moving recording paper to provide greater than usual detail. The text is brief, and the concepts are presented in concise fashion. This book is to be recommended as another source of concise information on catheterization, but many of the problems are neglected, most to be learned only by experience. This book is worth while and will serve a useful purpose.

G. E. BURCH, M.D.

The Lung as a Mirror of Systemic Disease. By Eli H. Rubin, M.D. Price, $12.50. Pp. 288, with 92 illustrations. Charles C Thomas, Publisher, 301-327 E. Lawrence Ave., Springfield, Ill., 1956.

This book will benefit anyone concerned with internal medicine in general or the chest in particular, but only "reflects" a small segment of each of the numerous systemic diseases which involve the lung. This limitation may not be evident from the title but is apparent to Dr. Rubin. In the brief preface he states, ". . . the chest x-ray, the keystone of diagnosis of pulmonary disease, is a window not a portrait, and often mirrors passing events." Dr. Rubin has made a significant contribution by emphasizing the usefulness of this "window" and by categorizing what he sees therein.

A major difficulty in creating a text of this type is classifying the subject matter. For example, should the pulmonary manifestations be grouped according to their appearance and the diseases which they represent fitted in accordingly, or should the systemic diseases be classified on some basis and their individual pulmonary manifestations recorded? Dr. Rubin chooses the latter despite the necessity of repetition—when two or more diseases have similar pulmonary manifestations—which such a choice necessarily entails. This provides the reader with a ready reference to the pulmonary changes in systemic diseases.

The text is frequently interspersed with numerous case reports. These are usually brief, always pertinent, and highly illustrative. Numerous chest roentgenograms are reproduced, and occasional gross and microscopic pathological specimens are illustrated. Photographic reproduction is excellent, and both author and publisher are to be commended for its high quality. At the end of each chapter there is an up-to-date, well-selected bibliography subdivided into the topics considered in that chapter.

Those portions of the text concerned with the histiocytoses and the collagen diseases, although scattered through several chapters, are among the best in this book. Considerable space is devoted to the nonpulmonary aspects of these diseases and their associated metabolic derangements and diagnostic features. Most of the other diseases mentioned are discussed in considerably less detail. The entire subject of reduced or absent γ-globulin and pulmonary infection is dismissed with the following sentence: "Pneumonia and bronchiectasis are also a feature of agammaglobulinemia because of poor antibody response to infection." This sentence concludes a brief section on myeloma. Unfortunately the interesting phenomonon of pulmonary infections occurring frequently when γ-globulin is increased or abnormal and also occurring with diminished or absent γ-globulin is not discussed further.

A considerable amount of space is devoted to such general categories as "Chest Roentgenography in Mass Surveys"; "Diagnosis: Symptoms and Signs"; "The Chest X-ray: Anatomical and Technical Considerations"; "Laboratory and Exploratory Aids," and others. Such information is included for the benefit of those not familiar with chest roentgenography and pulmonary diseases, for whom it will be most helpful. These subjects are not considered in any great detail. Sputum examination and skin tests are mentioned for the diagnosis of fungous diseases, but the agglutination and complement-fixation reactions are not.

The experienced internist will find much of value and interest in this book but may consider the material dealing with the nonpulmonary aspects of disease incomplete. The clinician experienced in lung disease may similarly criticize the sections on roentgen interpretation, laboratory procedures, physical examination, etc. Both will agree that Dr. Rubin has done a splendid job of correlating intrathoracic events with those occurring elsewhere in the body in a large number of disease states.

DAVID W. CUGELL, M.D.

Blakiston's New Gould Medical Dictionary. Edition 2. Edited by Norman L. Hoerr, M.D., and Arthur Osol, Ph.D., with the cooperation of an editorial board and 88 contributors. Price, $11.50. Pp. 1464, with numerous illustrations. Blakiston Division, McGraw-Hill Book Company, Inc., 330 W. 42d St., New York 36, 1956.

"After all, there is no such literature as a dictionary"—William Osler.

Reviewing a medical dictionary is not unlike taking on the phone book of New York City. There is so little about much in it that concentration on any one fact, name, or aspect, at best is only casually selective and cannot possibly be representative. Keeping any medical dictionary up-to-date in these rapidly changing times is a labor of love and requires the compulsive drives of editors with a strong, obsessive nature and much physical strength. In spite of Osler's merry words, I am not able to sit down and in cold blood read through a dictionary. I have now used this new dictionary for a number of weeks and have found it very satisfactory. It is cross referenced so that even when an occasional point is not available where first looked for, it can be found by back tracking or getting a new scent. The format of the book is attractive, but like all contemporary medical dictionaries, it has gotten too big to hold conveniently unless used on a table. The extensive aids to pronunciation will be very helpful in settling arguments and keeping us on the right track.

The numerous illustrative plates gathered together near the middle of the book would be somewhat more useful if they were placed under the appropriate heading in alphabetical order. The same is true of the tables and appendices, some of which at any rate might well be incorporated in the body of the book rather than relegated to a back seat.

For interest, I compared this dictionary with "Dunglison's Medical Dictionary" which was the American medical dictionary a hundred years ago. I found that the differences were so great that any satisfactory comparison would require detailed study. The almost infinite number of new words which have been introduced unfortunately far overbalances the number of words which have fallen into discard. But actually two different medical worlds are being defined. The selection of the names of living people for incorporation into the dictionary will interest and please those who are included and perhaps annoy those who may think they should have been but were not. It remains a matter of judgment, and since there is no consensus about a good many of the names, it might be well to wait until the person dies before one is included in the dictionary. This personal flavor and the strong representation of Cleveland in the

editorial staff gives it an individual tone. I can think of no more thankless task than trying to keep any dictionary up-to-date. All in all, this is a very satisfactory book and one in which the editors and printers can take legitimate pride.

WILLIAM B. BEAN, M.D.

Clinical Recognition and Management of Disturbances of Body Fluids. Edition 2. By John H. Bland. Price, $11.50. Pp. 522, with 109 illustrations. W. B. Saunders Company, 218 W. Washington Sq., Philadelphia 5; 7 Grape St., Shaftesbury Ave., London, W. C. 2, 1956.

The author seeks to provide the clinician with a practical pathophysiologic interpretation of the subject for bedside use. Unfortunately, the organization is poor, and there is a great deal of repetition. Too much space is given to defining objectives and not enough to a clear explanation of the steps leading to those objectives. There are a series of illustrations depicting various body spaces with trap doors, faucets, ladders, and treadmills, plus many little ionic men making entrances, exits, climbing stairs, swimming, etc. There are other diagrams depicting a wide variety of conditions in which specific numerical values are given for all of the ions in plasma, interstitial water, and intracellular water. At another point, forty-two types of intravenous fluids are diagrammed. Not only has the author made the subject more complex than it needs to be, but frequent erroneous statements are made. For example, he states that Ringer's solution, because of its calcium and potassium content, has greater efficacy in the treatment of metabolic acidosis. Actually, Ringer's solution is an acidifying solution because of its high chloride content and should never be used in the treatment of acidosis. In the chapter on shock, the author states that the efficacy of whole blood in the treatment of shock is due to the space-taking quality of the red blood cell. He says the main usefulness of intra-arterial transfusion is as a resuscitative measure when the heart has stopped. He says that adrenocortical steroids are capable of tiding the patient over between hemorrhage and whole-blood replacement. Such questionable statements are contradicted by statements and discussions made in other portions of the book, but it is left to the reader to decide which statements are true and which are false.

Much is written which has no real meaning. As an example, in support of his thesis that bedside observations deserve greater attention, the following statement is presented: "The retinal venules provide an interesting observation. Certainly not enough observations have been made to draw any conclusions, but I have looked at 150 patients' fundi and find that the retinal vein pulsation can be seen on funduscopic examination in 82% of this group. In three patients in whom there was a contracted plasma volume, hypotonic dehydration, and sodium depletion shock, the retinal vein pulsation could not be seen. Certainly one cannot say whether this is really useful but it is at least interesting to make this observation and it can be readily made if one is simply looking for it." Another example of meaningless wordage is the following explanation: "When . . . disease tosses a chemical monkey wrench into the metabolic gears of either extracellular water of intracellular water, a serious illness results." The author makes repeated statements about the need for "people who simply look, inquire and think as they see patients." He says that "most patients are handled far from the ivory towers and their photometers, Geiger counters and isotopes." Such statements give information only about their author.

There are two chapters which show a startling contrast to the remainder of the book by their organization, clearness, objectivity, and informative style. One is on water and electrolyte metabolism in pediatric patients in health and disease and the other is on surgical metabolism. A great deal of effort has gone into this revision. The 598 references and extensive index containing authors' names and subjects is of value.

EDWARD E. MASON.

Diseases of the Liver. Edited by Leon Schiff. Price, $16. Pp. 738. J. B. Lippincott Company, 227-231 S. 6th St., Philadelphia 5; 2083 Guy St., Montreal, 1956.

This book, in every sense a good book on diseases of the liver, opens with a chapter on anatomic considerations, by Rappaport, that is well done and illustrated with beautiful histologic pictures. The following chapters on biochemical considerations, by Seligson, and on experimental hepatic injury, by Hartroft, are excellent, although they might be difficult reading for the uninitiated in biochemistry. The authors have pointed

out many things left to be done and have tended to confirm, as much as anything, an old saying among those interested in hepatic disease—that the soul must be in the liver. Maclagen's discussion on tests of liver function is down to earth and practical, while Davidson's chapter on hepatic coma is a classic by one who has had great experience in this field. Smetana's review of the pathologic aspects of hepatitis is a magnificent article with excellent illustrations, both colored and black and white. The chapters on toxic hepatitis by Klatskin comprise one of the most complete discussions of chemical agents producing hepatic injury that one could hope to find. Patek's chapters on portal and postnecrotic cirrhosis, Kunkel's on biliary cirrhosis, Neefe's on viral hepatitis, and Althausen and Sborov's on hemochromatosis are all fine summaries of these conditions. Of considerable current interest is portal hypertension, which is discussed by Linton, and Sheila Sherlock's writing on the liver in circulatory failure is done completely and in her usual good style.

Other chapters on biopsy of the liver, jaundice, Wilson's disease, tumors of the liver, hepatic abscess, hepatic diseases in infancy and childhood, amyloid, syphilis and parasitic diseases of the liver, and diseases of the gall bladder and extrahepatic bile ducts are all done well.

This book is a fine example of good cooperation by a number of persons interested in a given field but with wide disciplines. The book has good paper, fine illustrations, and print which is most comfortable to read. References are generous and complete, and errors, typographical or other, are few. All in all, it is an example of good judgment by the editor in bringing together a group of specialists who are willing to write extremely careful articles in fields of their particular interest. The editor and the authors are to be congratulated. The book is recommended highly not only for those interested in diseases of the liver but also for those with more general interests.

HUGH R. BUTT, M.D.

Physical Diagnosis. By Ralph H. Major, M.D., and Mahlon H. Delp, M.D. Edition 5. Price, $7. Pp. 358, with 535 illustrations. W. B. Saunders Company, 218 W. Washington Sq., Philadelphia 5; 7 Grape St., Shaftesbury Ave., London, W. C. 2, 1956.

Beginning with the widespread use of x-ray examination of the chest in clinical medicine there seems to have been a decline in the emphasis on physical diagnosis in teaching medical students and in the practice of medicine. Several factors can be assigned for this trend. In demonstrating early lesions of the pulmonary parenchyma the superior accuracy of the roentgenologic film exposed the inefficiency of some of the classical physical signs developed so laboriously by Auenbrugger, Laennec, and others by comparison with the findings at the autopsy table. The vast progress in the physiologic aspects of disease multiplied the laboratory tests available for diagnosis. The medical practitioner, who by disuse had lost his ability to diagnose lesions of the cardiac valves, rationalized the situation by consoling himself that it was only an academic question as far as the patient was concerned. The busy physician found that he could see more patients in an hour by skimping or skipping the physical examination and sending them to the laboratory for a series of tests. The quality of the teaching of physical diagnosis in many medical schools was impaired because the senior members of the staffs were more interested in "scientific medicine" and assigned the task of teaching the subject to younger, inexperienced personnel. As a result, a definite tendency has emerged of relying less and less on the physical findings and more on the laboratory results as expressed in mathematical terms, which somehow always seem more convincing whether they are or not. The inexperienced physician attempts diagnosis by the "shotgun" method of ordering as many tests as he can think of in the hope that some result will turn up which will provide a clue to the problem. Frequently this is a tacit expression of his lack of confidence in his ability in physical diagnosis.

Recent developments, however, make a reversal of this trend imperative. The cost of medical care is increasing rapidly, and the public, rightly or wrongly, ascribe this to the medical profession. The ability of the diagnostician should be judged not only by his accuracy but by the cost to the patient in laboratory fees. It is cheaper to make diagnoses by the skillful elicitation of physical signs than by the accumulation of negative results from extensive roentgenologic examinations and blood chemical determinations. With the development of cardiac surgery it is no longer merely an "academic" question as to whether the patient has mitral stenosis or mitral insufficiency.

Progress in diagnostic procedures has thrown new light on the problems of physical diagnosis. Cardiac catheterization, fluoroscopic examination, and subsequent exploration of the heart at operation have resulted in a reaffirmation of confidence in the careful physical examination of the cardiovascular system. The availability of the cardioscope has been of distinct assistance in teaching auscultation of the heart to medical students. There is an increasing realization in medical faculties that the teaching of physical diagnosis should include participation by surgeons and other clinical specialists; the subject should not be limited to the field of internal medicine. A reemphasis on the teaching of physical diagnosis seems therefore indicated.

In the selection of a textbook for teaching physical diagnosis one is confronted with choices in two categories. There are a number which treat the subject as a separate discipline in which the emphasis is primarily on methodology. In general, these books are relatively small in size. The other category embraces texts in which the attempt is made to integrate the physical findings with laboratory tests or detailed accounts of the physiologic or pathologic background. These books are larger in size. Another cause of bulk is the inclusion of all physical signs which have grown up in medicine in the last 150 years, regardless of the fact that many have been discarded as impractical. A long experience in teaching has impressed me with the superiority of the shorter type of text. The sophomore medical student gets lost when confronted with too much detail. At the stage of his development his primary purpose should be to learn methodology of the physical examination. He must learn to observe, to feel, and to listen, requirements with which he has not coped before in his entire formal academic education. It takes considerable time to learn this, and he is fortunate if he has acquired facility before he graduates.

The book of Major and Delp belongs to the category of short books. It went through four editions with continuous improvement. The present, and fifth, edition contains the results of more radical revision, all further improvements. Dr. Delp has become associated with the work as co-author. The pages have been slightly increased in size, and the text has been thrown into two columns on the page. This has yielded a threefold advantage in that the number of pages has been actually diminished, the illustrations have been fitted into the pages with less waste of space, and the text is easier to read. Many pictures of the older editions have been replaced by better ones, so that most of the illustrations are excellent. Many good tracings of phonograms of heart sounds, murmurs, breath sounds, and percussion notes add considerably to the clarity of exposition. Short pertinent references to medical history have been included in pleasing and unobstrusive fashion. One could wish that Dr. Major had indulged his great knowledge of medical history a little more, but he wisely did not let it intrude on the main purpose of the book.

The organization of the material is excellent. The chapter on history-taking has been improved and moved to the front of the book. I found only minor items to criticize. For some curious reason the signs of auricular flutter are omitted. There is no statement of the fact that premature contractions tend to disappear with acceleration of the heart rate. One wishes that the physiologic mechanisms of some physical signs could have been more fully explained. The text is highly recommended for the teaching of physical diagnosis according to my philosophy.

ELMER L. DEGOWIN, M.D.

BOOKS RECEIVED

Ciba Foundation Colloquia on Endocrinology: Volume 9. Internal Secretions of the Pancreas. Edited by G. E. W. Wolstenholme, O.B.E., M.A., M.B., B.Ch., and Cecilia M. O'Connor, B.Sc. Price, $7. Pp. 292, with 100 illustrations. Little, Brown & Company, 34 Beacon St., Boston 6, 1956.

Ciba Foundation Colloquia on Ageing: Volume 2. Ageing in Transient Tissues. Edited by G. E. W. Wolstenholme, O.B.E., M.A., M.B., B.Ch., and Elaine C. P. Millar, approximately 60 illustrations. University of Minnesota Press, Minneapolis 14, 1956. A.H.W.C., A.R.I.C. Price, $6.75. Pp. 263, with 96 illustrations. Little, Brown & Company, 34 Beacon St., Boston 6, 1956.

The Nature of Brucellosis. By Wesley W. Spink, M.D., D.Sc. Price, $8. Pp. 464, with approximately 60 illustrations. University of Minnesota Press, Minneapolis 14, 1956.

Management of Strokes. By Keith W. Sheldon, M.D. Price, $3. Pp. 134, with 52 illustrations. J. B. Lippincott Company, 227-231 S. 6th St., Philadelphia 5, 1956.

A Dictionary of Dietetics. By Rhoda Ellis, Ph.D. Price, $6. Pp. 152, with no illustrations. Philosophical Library, Inc., 15 E. 40th St., New York 16, 1956.

The Office Assistant in Medical or Dental Practice. By Portia M. Frederick and Carol Towner. Price, $4.75. Pp. 351, with 55 illustrations. W. B. Saunders Company, 218 W. Washington Sq., Philadelphia 5, 1956.

The Management of Menstrual Disorders. By C. Frederick Fluhman, B.A., M.D., C.M. Price, $8.50. Pp. 350, with 121 illustrations. W. B. Saunders Company, 218 W. Washington Sq. Philadelphia 5, 1956.

Anesthesia for Obstetrics, Labor—Delivery—Infant Care. By Robert A. Hingson and Louis M. Hellman. Price, $12.50, Pp. 344. J. B. Lippincott Company, 227-231 S. 6th St., Philadelphia 5, 1956.

Annual Review of Medicine. Vol. 7. Edited by David A. Rytand and William Creger. Price, $7. Pp. 611. Annual Reviews, Inc., Stanford, Calif. 1956.

Cytology of the Blood and Blood-Forming Organs. By Marcel Bessis; translated by Eric Ponder. Price, $22. Pp. 629, with 404 illustrations and 22 color plates. Grune & Stratton, Inc., 381 Fourth Ave., New York 16; 99 Great Russell St., London, W.C. 1, 1956.

Ciba Foundation Symposium Jointly with The Physiological Society and The British Pharmacological Society on Histamine. Edited by G. E. W. Wolstenholme, O.B.E., M.A., M.B., B.Ch., and Cecilia M. O'Connor, B.Sc. Price, $9. Pp. 472, with 133 illustrations. Little, Brown and Company, 34 Beacon St., Boston 6, 1956.

Virus Diseases and the Cardiovascular System: A Survey. By Ernest Lyon, M.D. Price, $5.75. Pp. 215, with no illustrations. Grune & Stratton, Inc., 381 Fourth Ave., New York 16; 99 Great Russell St., London, W.C. 1, 1956.

Meditations on Medicine and Medical Education, Past and Present. By I. Snapper, M.D. Price, $3.75. Pp. 138, with no illustrations. Grune & Stratton, Inc., 381 Fourth Ave., New York 16; 99 Great Russell St., London, W.C. 1, 1956.

Synopsis of Gynecology: Based on the Textbook Diseases of Women. By Robert James Crossen, M.D., F.A.C.S. Price, $5.25. Pp. 255, with 132 illustrations and 1 color plate. C. V. Mosby Company, 3207 Washington Blvd., St. Louis 3, 1956.

Advances in Internal Medicine. Volume VIII. Edited by Dr. William Dock and Dr. I. Snapper. Price, $9. Pp. 366, with 23 illustrations and several tables. The Year Book Publishers, Inc., 200 E. Illinois St., Chicago 11, 1956.

The Morphology of Human Blood Cells. By Dr. L. W. Diggs, Dorothy Sturm, and Ann Bell, B.A. Price, $12. Pp. 181, with 54 illustrations and 21 color plates. W. B. Saunders Company, 218 W. Washington Sq., Philadelphia 5, 1956.

Cardiac Pressures and Pulses. By Dr. Aldo A. Luisada and Dr. Chi Kong Liu. Price, $6. Pp. 116, with 51 charts and several tables. Grune & Stratton, Inc., 381 Fourth Ave., New York 16; 99 Great Russell St., London, W.C. 1, 1956.

Physical Diagnosis. By Dr. Ralph H. Major and Dr. Mahlon H. Delp. Price, $7. Pp. 358, with 536 illustrations. W. B. Saunders Company, 218 W. Washington Sq., Philadelphia 5, 1956.

L'Activité électrique auriculaire normale et pathologique. By Dr. Paul Puech. Price, 2600 fr. Pp. 286, with 85 charts and 9 tables. Masson & Cie, 120 boulevard Saint-Germain, Paris, 6e, 1956.

Progress in Hematology. Volume 1. Edited by Dr. Leandro M. Tocantins; 27 contributors. Price, $9.75. Pp. 336, profusely illustrated. Grune & Stratton, Inc., 381 Fourth Ave., New York 16; 99 Great Russell St., London, W.C. 1, 1956.

The Year Book of Endocrinology (1955-1956 Year Book Series). Edited by Gilbert S. Gordon. Price, $6. Pp. 392. The Year Book Publishers, Inc., 200 E. Illinois St., Chicago 11, 1956.

Metabolism and Function of Iron. Report of the Nineteenth Ross Pediatric Research Conference. Edited by Samuel J. Famon, M.D. Price, not given. Pp. 93 (paper bound). Ross Laboratories, Columbus 16, Ohio, 1956.

The Practice of Psychosomatic Medicine, as Illustrated in Allergy. By Hyman Miller, M.D., and Dorothy W. Baruch, Ph.D. Price, $5. Pp. 196. McGraw-Hill Book Company, Inc., 330 W. 42d St., New York 36, 1956.

The Year Book of Pathology and Clinical Pathology (1955-1956 Year Book Series). Edited by William B. Wartman, B.S., M.D. Price, $6.50. Pp. 480, with 160 illustrations. The Year Book Publishers, Inc., 200 E. Illinois St., Chicago 11.

Atlas of Exfoliative Cytology. Supplement 1. By George N. Papanicolaou. Price, $4. Pp. 43, with 15 color plates. Published for The Commonwealth Fund by Harvard University Press, 44 Francis Ave., Cambridge 38, Mass., 1956.

Klinik der einheimischen Infektionskrankheiten. By Prof. Dr. W. Grunke. Price, 51.60 DM. Pp. 460, with 177 illustrations. VEB Georg Thieme, Hainstr. 17/19 Aufg. C, Leipzig C. 1, 1956.

News and Comment

ANNOUNCEMENTS

Examinations by American Board of Nutrition.—The American Board of Nutrition will hold the next examinations for certification as a Specialist in Human Nutrition, in April, 1957, at Chicago. Candidates who wish to be considered for these examinations should forward applications to the Secretary's office not later than March 1. Application forms may be obtained from the Secretary, Otto A. Bessey, Environmental Protection Research Division, Quartermaster Research and Development Center, Natick, Mass.

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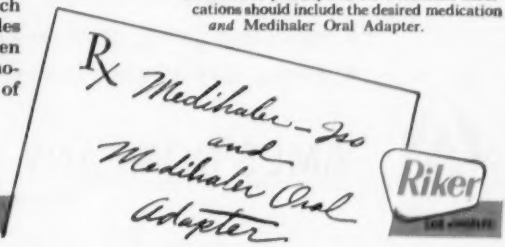

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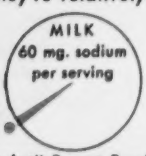

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Lemere, F.: Northwest Med. **54**: *1098, 1955.*

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Sokoloff, O.J.: A.M.A. Arch. Dermat. In press.

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Thimann, J. and Gauthier, J.W.: Quart. J. Stud. Alcohol. **17**: *19, 1956.*

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Borrus, J.C.: J.A.M.A. **157**: *1596, 1955.*

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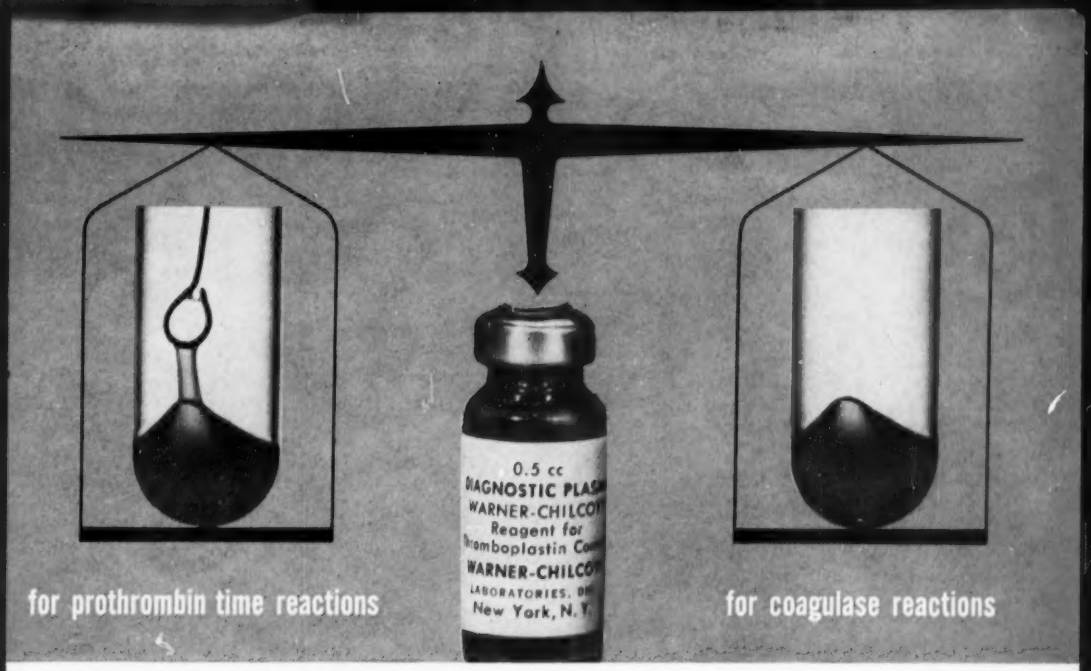

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References: 1. Tager, M.: Conference on Staphylococcal Infections, New York Academy of Sciences (Feb. 16) 1956. 2. Boyd, H.: First North American Conference of Medical Technology, Quebec (June 19) 1956.

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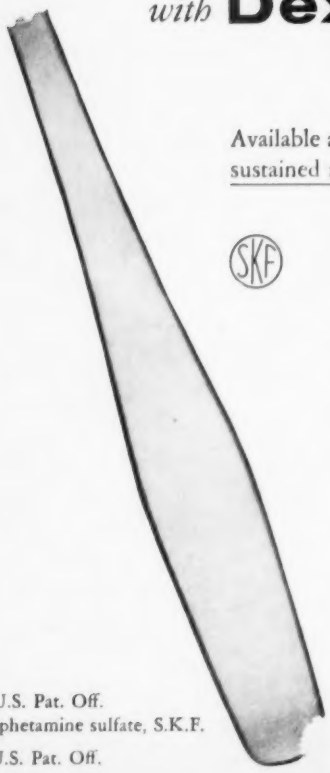

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